Multi-Omics Integration-Based Prioritisation of Competing Endogenous RNA Regulation Networks in Small Cell Lung Cancer: Molecular Characteristics and Drug Candidates

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Background: The competing endogenous RNA (ceRNA) network-mediated regulatory mechanisms in small cell lung cancer (SCLC) remain largely unknown. This study aimed to integrate multi-omics profiles, including the transcriptome, regulome, genome and pharmacogenome profiles, to elucidate prioritised ceRNA characteristics, pathways and drug candidates in SCLC.

Method: We determined the plasma messenger RNA (mRNA), microRNA (miRNA), long noncoding RNA (lncRNA) and circular RNA (circRNA) expression levels using whole-transcriptome sequencing technology in our SCLC plasma cohort. Significantly expressed plasma mRNAs were then overlapped with the Gene Expression Omnibus (GEO) tissue mRNA data (GSE 40275, SCLC tissue cohort). Next, we applied a multistep multi-omics (transcriptome, regulome, genome and pharmacogenome) integration analysis to first construct the network and then to identify the lncRNA/circRNA-miRNA-mRNA ceRNA characteristics, genomic alterations, pathways and drug candidates in SCLC.

Results: The multi-omics integration-based prioritisation of SCLC ceRNA regulatory networks consisted of downregulated mRNAs (CSF3R/GAA), lncRNAs (AC005005.4-201/DLX6-AS1-201/NEAT1-203) and circRNAs (hsa_HLA-B_1/hsa_VEGFC_8) as well as upregulated miRNAs (hsa-miR-4525/hsa-miR-6747-3p). lncRNAs (lncRNA-AC005005.4-201 and NEAT1-203) and circRNAs (circRNA-hsa_HLA-B_1 and hsa_VEGFC_8) may regulate the inhibited effects of hsa-miR-6747-3p for CSF3R expression in SCLC, while IncRNA-DLX6-AS1-201 or circRNA-hsa_HLA-B_1 may neutralise the negative regulation of hsa-miR-4525 for GAA in SCLC. CSF3R and GAA were present in the genomic alteration, and further identified as targets of Favld and
INTRODUCTION

Small cell lung cancer (SCLC) is a highly heterogeneous malignancy of neuroendocrine origin accounting for approximately 15% of all cases of lung cancer. SCLC is characterised by the early development of metastases, rapid recurrence and a low survival rate (1–4). The 5-year overall survival rate in SCLC barely reaches 5%, while average overall survival reaches only 2 to 4 months in untreated patients (1, 5, 6). Early diagnosis of SCLC remains quite challenging given its nonspecific symptoms and fast-growing tumours (7). Currently, chemotherapy and immunotherapy represent the most common treatment for SCLC, whereby chemotherapy alone remains the basis of standard treatment for the management of SCLC (7). While the initial response rate for first-line chemotherapy reaches approximately 60% in SCLC, patients may still quickly succumb to disease progression due to ineffective second-line treatment options (8–10). Thus, limited effective therapies remain the primary reason for poor outcomes in SCLC (7, 8). The mechanisms behind the pathogenesis of SCLC are complex, and as yet unexplained by a single biomarker or specific mechanism (11). As such, an increased and comprehensive understanding of SCLC characteristics is crucial to guiding both diagnosis and treatment. Omics studies are emerging rapidly and offer tremendous potential to better understand the underlying disease mechanisms, as well as advancing early diagnostics and identifying potential drug targets.

Competitive endogenous RNA (ceRNA) is a novel layer of gene regulation in diseases, regulating each other at the post-transcription level by competing for shared microRNAs (miRNAs) (12). ceRNA networks link the function of protein-coding messenger RNA (mRNA) with noncoding RNAs (ncRNAs), which primarily include long noncoding RNAs (lncRNAs), circular RNAs (circRNAs) and miRNAs (12–15). The integrative assessment of the expressions of lncRNAs, circRNAs, miRNAs and mRNAs construct ceRNA networks (14–18). Several studies demonstrated that lung cancer associates with the dysregulation of the expression of ncRNAs including both lncRNAs and miRNAs, and the expression of several signalling pathways and oncogenes, where circRNAs may play a key role in lung cancer tumorigenesis, progression, invasion and metastasis (14, 18). miRNAs could control the target genes involved in cellular processes by downregulating gene expression through repressing or degrading mRNA targets (19–21). In addition, the majority of lncRNAs compete with miRNAs to prevent miRNA binding to their target mRNA, leading to the transcriptional activation of target genes (22, 23). Furthermore, after binding to several sites for a particular miRNA or RNA-binding proteins (RBPs), circRNAs regulate alternative splicing and gene transcription through interaction (15, 23, 24). Consequently, these aberrantly expressed transcripts in the ceRNA network may represent potential therapeutic targets, diagnostic markers and prognostic markers in SCLC. In addition to transcriptomics, gene mutations play significant roles in new drug development in cancer. For instance, gene mutation profiles have facilitated the development of targeted agents in therapeutics for adenocarcinomas of the lung (25). Drug databases are developing rapidly, and the integrative analysis of omics data and drug databases provide us with excellent opportunities for drug development such as through pharmacogenomics (26). The rapidly expanding field of systems biology has proven reasonably effective at summarising knowledge related to cancer pathways, perhaps most importantly using the cancer literature to elucidate the molecular networks via which cancer develops. Thus, methodology which employs an integrative analysis of the literature could contribute to understanding the SCLC pathways (27).

In an attempt to understand the complexity and heterogeneity of SCLC, our study aimed to identify plasma mRNAs and compare them with the expression levels found in tissue to identify SCLC-specific mRNAs (28, 29) and, further, to evaluate the lncRNA/circRNA-miRNA-mRNA ceRNA regulatory network. Next, we applied a multi-omics integration analysis (transcriptome, regulome, genome and pharmacogenome) to discuss ceRNA regulation, genomic alterations, pathways and drug candidates in SCLC (see Figure 1) (30–32). Understanding the characteristics of the ceRNA regulatory network can potentially shed light on the screening of SCLC biomarkers, particularly those related to genomic alterations and novel therapeutic targets.

MATERIALS AND METHODS

In-House SCLC Plasma Cohort and SCLC Lung Tissue Cohort

In this study, we analysed two SCLC cohorts: an in-house SCLC plasma cohort (n = 12) and an SCLC lung tissue cohort (from GSE40275, n = 62) (33). The mRNA data in the SCLC tissue cohort were obtained from the lung tissue samples of SCLCs and adjacent nontumour regions. Our in-house SCLC plasma cohort includes...
Eight SCLC patients and four healthy controls, collected between August and November 2020 at Gansu Provincial Hospital, China. The inclusion criteria of patients in our SCLC plasma cohort consisted of a histologically or cytologically confirmed initial SCLC without previous chemotherapy, radiotherapy, molecular-targeted therapy, immunotherapy or surgery. We excluded patients from our SCLC plasma cohort based on the following: (1) presence of other combined cancers; (2) pregnant or lactating patient; and (3) presentation with cardiopulmonary insufficiency, serious cardiovascular disease, a serious infection or severe malnutrition (34, 35). The mRNA data in the SCLC tissue cohort were obtained from the lung tissue samples of SCLCs and adjacent nontumour regions. In addition, the tissue mRNA expression levels were evaluated in the Gene Expression Omnibus database (GEO, https://www.ncbi.nlm.nih.gov/gds/) using the term “small cell lung cancer” with “homo sapiens”, “series” and “expression profiling by array”. The 19 SCLC lung tissue datasets were obtained, and no suitable plasma SCLC dataset could be extracted. Finally, we selected the GSE40275 tissue dataset of SCLC for further analysis, since this dataset was obtained from a single-sequencing platform, thereby avoiding a potential bias from inconsistencies in probes stemming from different sequencing platforms. This cohort study received ethical approval from the Ethics Committee of the Gansu Provincial Hospital, China (27 July 2020, No. 2020-183). Informed consent was obtained from all participants in the whole-transcriptome sequencing experiment, and the research adhered to the principles of the Declaration of Helsinki.

**Whole-Transcriptome Sequencing Analysis in the Plasma SCLC Cohort**

We determined the plasma messenger RNA (mRNA), microRNA (miRNA), long noncoding RNA (lncRNA) and circular RNA (circRNA) expression levels using the whole-transcriptome sequencing technology in our SCLC plasma cohort. The extraction of total RNA from the plasma samples relied on the miRNeasy Mini Kit (Qiagen, Hilden, Germany) following the manufacturer’s protocol. The details appear in Supplemental File 1. A total of 1.5-μg RNA per sample was used as the input material for the lncRNA sequencing analysis, and a total of 2.5-ng RNA was used as the input material for the miRNA sequencing analysis. The steps to generating the mRNA, lncRNA, circRNA and miRNA profiles appear in Supplemental File 2. In addition, our SCLC plasma data were uploaded to a public platform [uploaded to the Sequence Read Archive (SRA) database (BioProject PRJNA 759049 (miRNA data) and BioProject PRJNA 762578 (mRNA, lncRNA and circRNA data)].

**Identification of Differentially Expressed mRNA, miRNA, circRNA and lncRNA in SCLC**

The significant differentially expressed mRNAs (DEmRNAs) in the SCLC tissue cohort were identified by comparing SCLC lung tissue and adjacent nontumour tissue from SCLC using the GEO2R tools from the R package “limma” in GSE40275 ([|fold change (FC)| > 1.5, p < 0.05, and false discovery rate (FDR) < 0.2]), DEmRNAs in the SCLC plasma cohort were identified by comparing SCLC and healthy samples using the likelihood ratio test (LRT) in the R package “DESeq” ([|FC| > 1.5, p < 0.05]). Then, the commonly expressed DEmRNAs (Co-DEmRNAs, SCLC-specific mRNAs) were defined as the overlapping DEmRNAs between the SCLC plasma cohort and the SCLC lung tissue cohort ([|FC| > 1.5, p < 0.05]). The significant DEmiRNAs, DEcircRNAs and DElncRNAs in the SCLC plasma cohort were identified by comparing SCLC and healthy plasma samples using...
LRT in the R package “DESeq” ([FC] > 1.5, p < 0.05, and FDR < 0.2). FDR was computed using the methodology described by Benjamini and Hochberg (36). The volcano plots were created using the R package “ggplot2”. Finally, the Co-DEmRNAs, DEmiRNAs, DEcircRNAs and DElncRNAs were subsequently used in the ceRNA network construction.

**Construction of the IncRNA/circRNA-miRNA-mRNA ceRNA-Mediated Regulatory Network**

The previous step identifying the DEmiRNAs, DElncRNAs, DEcircRNAs and Co-DEmRNAs in SCLC was used to construct the IncRNA/circRNA-miRNA-mRNA ceRNA regulatory network. The regulome analysis was based on the targeted mRNA–miRNA, IncRNA–miRNA and circRNA–miRNA prediction using online analytical software tools. The targeted mRNAs of the miRNAs were predicted using two online analytical software tools: miRanda (version 3.3.a) (37) and TargetScanHuman database (version 5.0) (38). The targeted lncRNAs of the miRNAs were predicted using the online analytical software tools from the miRBase database (version 22.0) (37). The targeted circRNAs of the miRNAs were predicted using three online analytical software tools: RNAhybrid database (version 2.1.1) (39), miRanda (version 3.3.a) (40) and TargetScanHuman database (version 5.0) (38). The negative regulation of mRNA–miRNA, IncRNA–miRNA and circRNA–miRNA was selected in the further ceRNA network construction. Next, the lncRNAs, circRNAs and miRNAs were identified as known or novel using several analytical software tools: the gffcompare program (41), the circRNA identifier (CIRI) tool (42), the miRBase database (version 22.0) (37) and the miRDeep2 tools (43). Based on these results, we constructed the lncRNA/circRNA-miRNA-mRNA ceRNA regulatory network using the Cytoscape software (version 3.7.0) (44). Next, the differentially expressed lncRNA, circRNAs, miRNAs and mRNAs in the SCLC ceRNA network were analysed using the gene ontology (GO) analysis and the Kyoto Encyclopaedia of Genes and Genomes (KEGG) pathway analysis. For the GO analysis, the differentially expressed lncRNA, circRNAs, miRNAs and mRNAs were classified into three categories: biological process (BP), cellular component (CC) and molecular function (MF). The KEGG pathway analysis was performed to analyse the potential pathways enriched by the differentially expressed lncRNA, circRNAs, miRNAs and mRNAs. The enrichment analysis was evaluated using the R package ClusterProfiler (45), for which we considered an adjusted p < 0.05 as statistically significant (46).

**Evaluation of Genomic Alterations, Drug Candidates/Repurposing and Pathway Analysis in SCLC ceRNA Networks**

The genomic alterations of mRNAs in the SCLC ceRNA network were determined through three datasets (47–49) from the cBioPortal database (https://www.cbioportal.org/datasets), including the Clinical Lung Cancer Genome Project (CLCGP) study (47), the Johns Hopkins study (48) and the University of Cologne study (U Cologne study) (49). The pharmacogenomics data were downloaded from the DrugBank database (release 5.0) (https://go.drugbank.com/), including the rich drugs data and the drug–target genes data (50). The results obtained from the pharmacogenomics DrugBank database were further mined through the “Targets” tool using manual searches. The pathways of the mRNAs were first evaluated and annotated using the Genecards database (https://www.genecards.org/) (51), then the SCLC-associated pathways were further filtered through a literature search from PubMed (https://pubmed.ncbi.nlm.nih.gov/) using the terms “small cell lung cancer [Title/Abstract] OR SCLC [Title/Abstract] OR small cell lung cancer [MeSH Terms]” and “pathways [Title/Abstract]”.

**RESULTS**

**Identification of Differentially Expressed mRNA, miRNA, circRNA and IncRNA in SCLC**

We identified eight SCLC patients (62.5% male, median age of 62 years, 100% Asian and 50.0% advanced stage) and four healthy controls (75.0% male, median age of 66 years) in our SCLC plasma cohort, and 19 SCLC patients (84.2% male, median age of 66 years and 100% European) in the SCLC tissue cohort (GSE40275) (Table 1). Through our in-house whole-transcriptome sequencing data comparing SCLC plasma samples and healthy plasma samples, we harvested a total of 652 DEmRNAs (326 upregulated and 326 downregulated), 281 DEmiRNAs (178 upregulated and 103 downregulated), 286 DEcircRNAs (166 upregulated and 120 downregulated) and 1753 DElncRNAs (1036 upregulated and 717 downregulated) for subsequent analysis. Overall, 8429 DEMRNAs (4808 upregulated and 3621 downregulated) were identified in the SCLC tissue cohort, ultimately resulting in 135 DEMRNAs (32 upregulated and 103 downregulated) expressed in two cohorts as common DEMRNAs (Co-DEMRNAs), and also identified as SCLC-specific mRNAs (Figure 2).

**Construction of the IncRNA/circRNA-miRNA-mRNA ceRNA Network**

The obtained 281 DEMiRNAs, 1753 DElncRNAs, 286 DEcircRNAs and 135 Co-DEmRNAs in SCLC were initially involved in the ceRNA regulatory network construction. Integrating the selection rules described in the methods section, the SCLC IncRNA/circRNA-miRNA-mRNA ceRNA regulatory network was constructed, which included 58 mRNAs (4 upregulated and 54 downregulated), 301 lncRNAs (40 upregulated and 261 downregulated), 16 circRNAs (5 upregulated and 11 downregulated) and 24 miRNAs (20 upregulated and 4 downregulated) (Figures 3 and 4; Supplemental Tables 1 and 2). The IncRNA-miRNA-mRNA ceRNA regulatory network consisted of 381 nodes (301 IncRNAs, 23 miRNAs and 57 mRNAs) with 707 edges (Figure 3). In the IncRNA-miRNA-mRNA ceRNA network, the expression levels of 53 mRNAs and 261 lncRNAs decreased in SCLC and the expression levels of 19 miRNAs...
increased in SCLC, while the expression levels of 4 mRNAs and 40 IncRNAs increased in SCLC and the expression levels of 4 miRNAs decreased in SCLC (Supplemental Table 1). The circRNA-miRNA-mRNA ceRNA network consisted of 82 nodes (16 cirRNAs, 19 miRNAs and 47 mRNAs) with 165 edges (Figure 4). In the circRNA-miRNA-mRNA ceRNA network, the expression levels of 43 mRNAs and 11 cirRNAs decreased in SCLC and the expression levels of 16 miRNAs increased in SCLC, while the expression levels of four mRNAs and five cirRNAs increased in SCLC and the expression levels of three miRNAs decreased in SCLC (Supplemental Table 2).

**Functional Enrichment Analysis of mRNA, miRNA, circRNA and IncRNA in the ceRNA Network in SCLC**

The differentially expressed levels of 58 mRNAs in the ceRNA network appear in Table 2. In the SCLC plasma cohort, the top three downregulated genes in the fold change (FC) were early growth response 1 (EGR1), complement factor D (CFD) and FosB proto-oncogene AP-1 transcription factor subunit (FOSB), while the top three upregulated genes in FC were zinc finger protein 704 (ZNF704), NOVA alternative splicing regulator 1 (NOVA1) and attractin like 1 (ATRNL1) (Table 2). Table 3

**FIGURE 2** | Identification of differentially expressed mRNAs, miRNAs, IncRNAs and circRNAs in SCLC. (A) Common differentially expressed mRNAs (Co-DEmRNAs) in the in-house SCLC plasma cohort and the SCLC lung tissue cohort (GSE40275). (B) Up- and downregulated mRNAs in our cohort. (C) Up- and downregulated IncRNAs in our cohort. (D) Up- and downregulated circRNAs in our cohort. Red indicates upregulated and green indicates downregulated; circRNA, circular RNAs; IncRNA, long noncoding RNA; mRNA, microRNA; mRNA, messenger RNA; SCLC, small cell lung cancer.

### TABLE 1 | Patient characteristics for the in-house SCLC plasma cohort (n = 12) and SCLC lung tissue cohort (from GSE40275, n = 62).

| Patient characteristics | SCLC lung tissue cohort (GSE40275) | In-house SCLC plasma cohort |
|-------------------------|----------------------------------|---------------------------|
|                         | normal                          | SCLC patients             | normal                          | SCLC patients             |
| Age (median, in years)  | 66                              | 70                        | 66                              | 61.5                       |
| Sex (males, %)          | 19 (44.2%)                      | 16 (84.2%)                | 3 (75.0%)                       | 5 (62.5%)                  |
| Country                 | Austria                          | Austria                   | China                           | China                      |
| Ethnicity               | Austrian                         | Austrian                  | Asian                           | Asian                      |
| AJCC stage              | Stage I                          | 9 (47.4%)                 | –                               | 0                          |
|                         | Stage II                         | 4 (20.1%)                 | –                               | 1 (12.5%)                  |
|                         | Stage III                        | 6 (31.6%)                 | –                               | 3 (37.5%)                  |
|                         | Stage IV                         | 0                         | –                               | 4 (50%)                    |
| VALSG stage             | Extended stage                   | 0                         | –                               | 4 (50%)                    |
|                         | Limited stage                    | 16 (100%)                 | –                               | 4 (50%)                    |
| Outcome                 | Dead                             | NA                        | –                               | 8 (100%)                   |
|                         | Living                           | NA                        | –                               | D                          |

SCLC, small cell lung cancer; AJCC, American Joint Committee on Cancer; VALSG, Veterans Administration Lung Study Group.

NA, not available.

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summarises 23 results from 58 mRNAs in the ceRNA network included in the GO analysis. This GO analysis indicated that the DEmRNAs were associated with numerous important biological processes and cellular components. The present study indicated that the biological processes of DEmRNAs primarily included processes such as neutrophil degranulation, neutrophil activation involved in the immune response, neutrophil activation, neutrophil-mediated immunity and an integrin-mediated signalling pathway among others. These biological functions associate with the protumour/prometastatic roles of inflammatory cells in cancer development and metastasis (Table 3) (52, 53). In terms of the cellular components, they mainly included the protein complex involved in cell adhesion and the integrin complex (Table 3), functions associated with tumorigenesis (54, 55). In addition, no results were obtained from the molecular function of the GO analysis and the KEGG pathways analysis, given that adjusted $p > 0.05$ in these functional analyses. In addition, we also reported the differentially expressed levels of lncRNAs, circRNAs and miRNAs in the ceRNA network (Supplemental Tables 3-5). The functional GO analyses primarily revealed cell survival and proliferation in 42 functional results from 301 lncRNAs, the inflammatory and immune response function in 32 functional results from 32 circRNAs and inflammatory and immune response and cell proliferation in 66 functional results from 24 miRNAs, respectively (Tables 4–6). Among these functions, many tumour-related terms were significantly enriched, such as regulating the cell cycle, the negative regulation of cell growth,
| Gene symbol | Gene full name | Differentially expressed levels | Genomic alterations |
|-------------|----------------|-------------------------------|--------------------|
|             | In-house SCLC   | SCLC lung tissue cohort       |                    |
|             | plasma cohort   | (GSE40275)                   |                    |
|             | log2FC          | log2FC                        |                    |
|             | p value         | p value                       |                    |
| EGR1        | Early Growth   | -3.232                       | 3.0%               |
|             | Response 1      | -2.611                       | 0                   |
|             |                 | -3.42E-04                    | 16                 |
| CFD         | Complement Factor D | -2.898                    | 0                   |
|             |                 | -2.472                       | 0.8%               |
| ABCA2       | ATP Binding     | -2.814                       | 3.0%               |
|             | Cassette        | -1.923                       | 1.3%               |
|             | Subfamily A Member 2 | -3.00E-04              | 2.5%               |
| PRF1        | Perforin 1      | -2.699                       | 3.0%               |
|             |                 | -2.038                       | 0                   |
| STAB1       | Stabilin 1      | -2.484                       | 3.0%               |
|             |                 | -1.151                       | 0                   |
| AHNAK       | AHNK Nucleoprotein | -2.443                    | 7.0%               |
|             |                 | -2.761                       | 4.0%               |
|             |                 | 8.93E-06                     | 6.0%               |
| CD300E      | CD300e Molecule | -2.428                       | 0                   |
|             |                 | -1.009                       | 0                   |
|             |                 | 3.72E-05                     | 0.8%               |
| CD244       | CD244 Molecule  | -2.332                       | 3.0%               |
|             |                 | -0.751                       | 0                   |
|             |                 | 4.27E-14                     | 0.8%               |
| SLC27A1     | Solute Carrier | -2.331                       | 0                   |
|             | Family 27 Member 1 | -0.76                      | 0                   |
|             |                 | 6.68E-14                     | 1.7%               |
| PARP10      | Poly (ADP-Ribose) | -2.12                       | 3.0%               |
|             | Polymerase Family Member 10 | -0.601                  | 0                   |
|             |                 | 4.27E-14                     | 0.8%               |
| MEFV        | MEFV Innate Immunity Regulator, Pyrin | -2.051                  | 0                   |
|             |                 | -0.281                       | 1.3%               |
|             |                 | 6.27E-14                     | 1.7%               |
| RHBDF2      | Rhomboid 5 Homolog 2 | -2.028                    | 3.0%               |
|             |                 | -0.981                       | 0                   |
|             |                 | 5.62E-14                     | 0                   |
| DNAH1       | Dynein Axonemal Heavy Chain 1 | -2.02                     | 0                   |
|             |                 | -0.653                       | 0                   |
|             |                 | 2.07E-18                     | 7.0%               |
| TCIQG1      | T Cell Immune Regulator 1, ATPase H+ Transporting V0 Subunit A3 | -1.908                  | 0                   |
|             |                 | -1.421                       | 0                   |
|             |                 | 4.46E-17                     | 1.7%               |
| NFA1        | NFAT Activating Protein With ITAM Motif 1 | -1.976                  | 0                   |
|             |                 | -0.708                       | 0                   |
|             |                 | 2.61E-13                     | 0.8%               |
| Gill8P5     | GTPase, IMP Family Member 8 | -1.902                  | 10.0%              |
|             |                 | -2.078                       | 0                   |
|             |                 | 2.10E-31                     | 3.0%               |
| PLXN2       | Plexin B2       | -1.896                       | 7.0%               |
|             |                 | -1.904                       | 1.3%               |
|             |                 | 1.38E-09                     | 3.0%               |
| FGD2        | FYVE, PhoGEF And Ph Domain Containing 2 | -1.885                  | 0                   |
|             |                 | -1.386                       | 0                   |
|             |                 | 7.07E-19                     | 0.8%               |
| NLRP12      | NLR Family Pyrin Domain Containing 12 | -1.862                   | 7.0%               |
|             |                 | -0.852                       | 1.3%               |
|             |                 | 4.45E-16                     | 4.0%               |
| NOTCH1      | Notch Receptor | -1.848                       | 10.0%              |
|             | 1              | -1.497                       | 1.3%               |
|             |                 | 3.76E-22                     | 13.0%              |
| FCN1        | Ficolin 1       | -1.844                       | 0                   |
|             |                 | -1.675                       | 0                   |
|             |                 | 3.00E-23                     | 2.5%               |
| CSF3R       | Colony-stimulating factor 3 receptor | -1.801                  | 7.0%               |
|             |                 | -2.468                       | 1.3%               |
|             |                 | 2.01E-29                     | 2.5%               |
| GAA         | Acid alpha-glucosidase | -1.789                    | 3.0%               |
|             |                 | -1.108                       | 1.3%               |
|             |                 | 2.59E-13                     | 2.5%               |
| ITGB2       | Integrin Subunit Beta 2 | -1.756                    | 3.0%               |
|             |                 | -1.813                       | 0                   |
|             |                 | 1.25E-11                     | 2.5%               |
| EMLIN2      | Elastin Microfibril Interfac 2 | -1.748                   | 0                   |
|             |                 | -1.372                       | 2.5%               |
|             |                 | 1.79E-18                     | 2.5%               |
| ARHGP4      | Rho GTPase Activating Protein 4 | -1.741                  | 3.0%               |
|             |                 | -0.624                       | 1.3%               |
|             |                 | 3.80E-07                     | 4.0%               |
| CD93        | CD93 Molecule   | -1.722                       | 3.0%               |
|             |                 | -2.668                       | 0                   |
|             |                 | 4.54E-34                     | 1.7%               |
| DAPK1       | Death Associated Protein Kinase 1 | -1.707                   | 3.0%               |
|             |                 | -1.123                       | 2.5%               |
|             |                 | 5.50E-06                     | 4.0%               |

(Continued)
| Gene symbol | Gene full name | Differentially expressed levels | Genomic alterations |
|-------------|----------------|---------------------------------|--------------------|
|             |                | In-house SCLC plasma cohort | SCLC lung tissue cohort (GSE40275) | Regulated | CLCGP, Nat Genet 2012 | Johns Hopkins, Nat Genet 2012 | U Cologne, Nature 2015 |
|             |                | log2FC | p value | log2FC | p value |                |                   |                    |
| TTC7A       | Tetratricopeptide Repeat Domain 7A  | -1.651 | 2.83E-02 | -1.265 | 3.85E-11 | down          | 0                  | 1.3%               | 2.5%               |
| PSD4        | Pleckstrin And Sec7 Domain Containing 4 | -1.632 | 1.74E-02 | -0.802 | 3.80E-11 | down          | 3.0%               | 1.3%               | 3.0%               |
| CITA        | Class II Major Histocompatibility Complex Transactivator | -1.624 | 2.17E-02 | -1.777 | 3.50E-11 | down          | 0                  | 1.3%               | 0                  |
| SYNE1       | Spectrin Repeat Containing Nuclear Envelope Protein 1 | -1.606 | 3.16E-03 | -1.689 | 1.78E-19 | down          | 28.0%              | 11.0%              | 23.0%              |
| ITGAX       | Integrin Subunit Alpha X | -1.592 | 1.15E-02 | -2.083 | 9.75E-18 | down          | 3.0%               | 1.3%               | 3.0%               |
| ADAMTS4     | ADAMTS Like 4  | -1.555 | 3.60E-02 | -1.606 | 2.64E-22 | down          | 0                  | 0                  | 2.5%               |
| XAF1        | XIAP Associated Factor 1 | -1.552 | 1.88E-02 | -1.445 | 3.44E-10 | down          | 3.0%               | 1.3%               | 0                  |
| FGR         | FGR Proto-Oncogene, Src Family Tyrosine Kinase | -1.488 | 2.02E-02 | -2.179 | 5.88E-12 | down          | 0                  | 2.5%               | 0.8%               |
| PLCB2       | Phospholipase C Beta 2 | -1.474 | 1.89E-02 | -1.634 | 8.74E-19 | down          | 0                  | 1.3%               | 0                  |
| APLP2       | Amyloid Beta Precursor Like Protein 2 | -1.47 | 2.22E-02 | -0.935 | 5.30E-17 | down          | 5.0%               | 2.5%               | 0                  |
| AKNA        | AT-Hook Transcription Factor | -1.467 | 4.69E-02 | -1.126 | 7.99E-20 | down          | 7.0%               | 2.5%               | 1.7%               |
| RNF213      | Ring Finger Protein 213 | -1.452 | 1.46E-02 | -0.714 | 8.47E-06 | down          | 0                  | 4.0%               | 2.5%               |
| HHERC3      | HECT And RLD Domain Containing E3 Ubiquitin Protein Ligase 3 | -1.45 | 4.01E-02 | -0.725 | 1.92E-16 | down          | 0                  | 0                  | 0.8%               |
| ARHGEF1     | Rho Guanine Nucleotide Exchange Factor 1 | -1.443 | 3.72E-02 | -0.724 | 6.38E-09 | down          | 0                  | 1.3%               | 2.5%               |
| MYO1F       | Myosin 1F | -1.394 | 4.04E-02 | -2.014 | 2.90E-09 | down          | 3.0%               | 1.3%               | 2.5%               |
| MYO1G       | Myosin 1G | -1.314 | 3.45E-02 | -1.526 | 3.29E-20 | down          | 3.0%               | 0                  | 1.7%               |
| ADCY7       | Adenylate Cyclase 7 | -1.314 | 3.64E-02 | -1.626 | 7.20E-23 | down          | 3.0%               | 0                  | 4.0%               |
| PARP14      | Poly(ADP-Ribose) Polymerase Family Member 14 | -1.233 | 4.09E-02 | -1.178 | 2.66E-08 | down          | 0                  | 0                  | 2.5%               |
| ITGAL       | Integrin Subunit Alpha L | -1.225 | 3.83E-02 | -1.893 | 6.98E-17 | down          | 3.0%               | 0                  | 5.0%               |
| ZNF704      | Zinc Finger Protein 704 | Inf | 2.00E-02 | 1.059 | 8.34E-13 | up            | 0                  | 0                  | 0.8%               |
| NOVA1       | NOVA Alternative Splicing Regulator 1 | Inf | 3.63E-02 | 1.039 | 2.61E-16 | up            | 0                  | 1.3%               | 1.7%               |
| ATRNL1      | Attractin Like 1 | Inf | 3.34E-02 | 0.878 | 6.12E-09 | up            | 7.0%               | 4.0%               | 3.0%               |

No genomic alterations (n = 8)

| FOSB | FosB Proto-Oncogene, AP-1 Transcription Factor Subunit | -3.723 | 4.45E-02 | -3.385 | 2.01E-15 | down | 0 | 0 | 0 |
| ADAM15 | ADAM Metalloproteinase Domain 15 | -3.479 | 1.29E-02 | -0.586 | 4.13E-08 | down | 0 | 0 | 0 |
| KLF6 | Kruppel Like Factor 6 | -1.999 | 4.21E-03 | -1.665 | 3.59E-18 | down | 0 | 0 | 0 |
| IL10RA | Interleukin 10 Receptor Subunit Alpha | -1.921 | 2.54E-03 | -1.772 | 8.82E-14 | down | 0 | 0 | 0 |
| ATG16L2 | Autophagy Related 16 Like 2 | -1.851 | 0.01755 | -0.665 | 1.89E-12 | down | 0 | 0 | 0 |

(Continued)
TABLE 2 | Continued

| Gene symbol | Gene full name | Differentially expressed levels | Genomic alterations |
|-------------|----------------|----------------------------------|---------------------|
|             |                | In-house SCLC                      | SCCL lung tissue cohort (GSE40275) | Regulated | CLCGP, Nat Genet 2012 | Johns Hopkins, Nat Genet 2012 | U Cologne, Nature 2015 |
|             |                | log2FC | p value | log2FC | p value | down | 0 | 0 | 0 |
| MYO15B      | Myosin XVB     | -1.814 | 4.40E-02 | -0.837 | 1.26E-12 | down | 0 | 0 | 0 |
| IRF1        | Interferon Regulatory Factor 1 | -1.589 | 8.63E-03 | -1.775 | 4.68E-11 | up | 0 | 0 | 0 |
| GREM1       | Gremlin 1, DAN Family BMP Antagonist | Inf | 4.60E-02 | 1.011 | 1.16E-08 | up | 0 | 0 | 0 |

SCLC, small cell lung cancer; circRNA, circular RNA; lncRNA, long noncoding RNA; miRNA, microRNA; mRNA, messenger RNA; ceRNA, competing endogenous RNA; FC, fold change; Inf, infinity; CLCGP, Clinical Lung Cancer Genome Project; U Cologne, University of Cologne study.

TABLE 3 | Functional enrichment analysis of mRNAs in the ceRNA network in SCLC.

| ID | Description | Ontology | Bg Ratio | p value | Adjusted p | Genes symbol* | Count |
|----|-------------|----------|----------|---------|------------|---------------|-------|
| GO:0043312 | neutrophil degranulation | BP | 485/18670 | 1.843E-06 | 9.114E-04 | CFD/FCN1/FGR/GAA/ITGAL/ITGAX/ITGB2/TCIRG1/CD93/NFAM1 | 10 |
| GO:0002283 | neutrophil activation involved in immune response | BP | 485/18670 | 1.948E-06 | 9.114E-04 | CFD/FCN1/FGR/GAA/ITGAL/ITGAX/ITGB2/TCIRG1/CD93/NFAM1 | 10 |
| GO:0042119 | neutrophil activation | BP | 498/18670 | 1.161E-08 | 9.114E-04 | CFD/FCN1/FGR/GAA/ITGAL/ITGAX/ITGB2/TCIRG1/CD93/NFAM1 | 10 |
| GO:0002446 | neutrophil-mediated immunity | BP | 499/18670 | 1.011E-08 | 9.114E-04 | CFD/FCN1/FGR/GAA/ITGAL/ITGAX/ITGB2/TCIRG1/CD93/NFAM1 | 10 |
| GO:0007229 | integrin-mediated signalling pathway | BP | 103/18670 | 1.545E-05 | 4.738E-02 | CFD/FCN1/FGR/GAA/ITGAL/ITGAX/ITGB2/TCIRG1/CD93/NFAM1 | 10 |
| GO:0050663 | cytokine secretion | BP | 240/18670 | 2.272E-02 | 2.272E-02 | CFD/FCN1/FGR/GAA/ITGAL/ITGAX/ITGB2/TCIRG1/CD93/NFAM1 | 10 |
| GO:0030198 | extracellular matrix organization | BP | 368/18670 | 2.467E-02 | 2.467E-02 | CFD/FCN1/FGR/GAA/ITGAL/ITGAX/ITGB2/TCIRG1/CD93/NFAM1 | 10 |
| GO:0050900 | leukocyte migration | BP | 499/18670 | 2.467E-02 | 2.467E-02 | CFD/FCN1/FGR/GAA/ITGAL/ITGAX/ITGB2/TCIRG1/CD93/NFAM1 | 10 |
| GO:0043062 | extracellular structure organization | BP | 422/18670 | 4.873E-02 | 4.873E-02 | CFD/FCN1/FGR/GAA/ITGAL/ITGAX/ITGB2/TCIRG1/CD93/NFAM1 | 10 |
| GO:0101003 | ficolin-1-rich granule membrane | CC | 61/19717 | 6.558E-05 | 6.558E-05 | CFD/FCN1/FGR/GAA/ITGAL/ITGAX/ITGB2/TCIRG1/CD93/NFAM1 | 10 |
| GO:0101002 | ficolin-1-rich granule | CC | 185/19717 | 6.558E-05 | 6.558E-05 | CFD/FCN1/FGR/GAA/ITGAL/ITGAX/ITGB2/TCIRG1/CD93/NFAM1 | 10 |
| GO:0030667 | secretory granule membrane | CC | 308/19717 | 2.673E-02 | 2.673E-02 | CFD/FCN1/FGR/GAA/ITGAL/ITGAX/ITGB2/TCIRG1/CD93/NFAM1 | 10 |
| GO:0070820 | tertiary granule membrane | CC | 298/19717 | 9.263E-05 | 9.263E-05 | CFD/FCN1/FGR/GAA/ITGAL/ITGAX/ITGB2/TCIRG1/CD93/NFAM1 | 10 |
| GO:0008305 | integrin complex | CC | 31/19717 | 2.370E-03 | 2.370E-03 | CFD/FCN1/FGR/GAA/ITGAL/ITGAX/ITGB2/TCIRG1/CD93/NFAM1 | 10 |
| GO:0070820 | tertiary granule | CC | 164/19717 | 2.370E-03 | 2.370E-03 | CFD/FCN1/FGR/GAA/ITGAL/ITGAX/ITGB2/TCIRG1/CD93/NFAM1 | 10 |
| GO:0023843 | protein complex involved in cell adhesion | CC | 73/19717 | 1.890E-03 | 1.890E-03 | CFD/FCN1/FGR/GAA/ITGAL/ITGAX/ITGB2/TCIRG1/CD93/NFAM1 | 10 |
| GO:0006774 | vascular membrane | CC | 34/19717 | 1.286E-03 | 1.286E-03 | CFD/FCN1/FGR/GAA/ITGAL/ITGAX/ITGB2/TCIRG1/CD93/NFAM1 | 10 |
| GO:0031256 | leading edge membrane | CC | 170/19717 | 1.988E-02 | 1.988E-02 | CFD/FCN1/FGR/GAA/ITGAL/ITGAX/ITGB2/TCIRG1/CD93/NFAM1 | 10 |
| GO:0001726 | Ruffle | CC | 172/19717 | 1.988E-02 | 1.988E-02 | CFD/FCN1/FGR/GAA/ITGAL/ITGAX/ITGB2/TCIRG1/CD93/NFAM1 | 10 |
| GO:0035579 | specific granule membrane | CC | 91/19717 | 2.725E-02 | 2.725E-02 | CFD/FCN1/FGR/GAA/ITGAL/ITGAX/ITGB2/TCIRG1/CD93/NFAM1 | 10 |

(Continued)
DNA recombination and the MyD88-independent toll-like receptor signalling pathway, as well as the regulation of dendritic cell differentiation. In the KEGG pathways analyses, five pathways were identified in the lncRNAs, consisting of olfactory transduction, the neuroactive ligand–receptor interaction, nicotine addiction, carbohydrate digestion and absorption, and the protein digestion and absorption pathway (Table 7). The 60 pathways found in the miRNAs and mainly tumour-related pathways were significantly enriched, including the CAMP signalling pathway, focal adhesion, the MAPK signalling pathway, the Hippo signalling pathway and the ECM–receptor interaction (Table 7).

**Evaluation of Genomic Alterations, Drug Candidates/Repurposing and Pathways in SCLC ceRNA Network**

In total, 50 of 58 mRNAs in the ceRNA network presented genomic alterations, with the percentage of genomic alterations ranging from 0.8% to 28% (Table 2). The drug–target gene pharmacogenomics analysis showed that three [colony-stimulating factor 3 receptor (CSF3R)] alterations range 1.3–7.0%, FC (in plasma cohort): -1.801, FGR proto-oncogene Src family tyrosine kinase (FGR) (alterations range 3.5–3.0%, FC: -1.789 and p = 3.85 x 10^{-2}), FGR proto-oncogene Src family tyrosine kinase (FGR) (alterations range 0–2.5%, FC: -1.488, p = 2.02 x 10^{-2})] of 50 mRNAs in the ceRNA network were identified as potential drug targets (Tables 2 and 8). CSF3R and GAA were identified as targets of FavId and Trastuzumab deruxtecan, respectively, while FGR was confirmed as a target of Dasatinib and Zanubrutinib (Table 8). Next, the pathway analysis found that CSF3R, GAA and FGR were annotated in the 13 pathways in the Genecards database (Table 9). The SCLC-associated pathways were further identified through a literature review (56–58). We concluded that CSF3R was involved in the autophagy pathway and GAA was involved in the glucose metabolism pathway, while these two pathways were involved in SCLC occurrence and progression from the literature (Table 9) (56–58).

**Identification of Multi-Omics Integration-Based Prioritisation of the ceRNA SCLC Network**

The multi-omics integration-based prioritisation of the ceRNA regulatory network in SCLC consisted of two mRNAs, two miRNAs, three lncRNAs and two circRNAs (Figure 5). In this ceRNA network, the expression levels of mRNAs (CSF3R/GAA), miRNAs (hsa-miR-4525/hsa-miR-6747-3p), three lncRNAs (AC005005.4-201/DLX6-AS1-201/NEAT1-203) and circRNAs (hsa_HLA-B_1/hsa_VEGFC_8) decreased in SCLC, while the expression levels of miRNAs (hsa-miR-4525/hsa-miR-6747-3p) increased in SCLC. The primary regulatory axes in the ceRNA network were identified as follows: 1) lncRNA-miRNA-mRNA: AC005005.4-201/NEAT1-203-hsa-miR-6747-3p-CSF3R and DLX6-AS1-201-hsa-miR-4525-GAA; and 2) circRNA-miRNA-mRNA: hsa_HLA-B_1/hsa_VEGFC_8-hsa-miR-6747-3p-CSF3R and hsa_HLA-B_1-hsa-miR-4525-GAA (Figure 5). Thus, lncRNAs (IncRNA-AC005005.4-201 and NEAT1-203) and circRNAs (circRNA-hsa_HLA-B_1 and hsa_VEGFC_8) may regulate the inhibited effects of hsa-miR-6747-3p for CSF3R expression in SCLC, and lncRNA-DLX6-AS1-201 or circRNA-hsa_HLA-B_1 may neutralise the negative regulation of hsa-miR-4525 for GAA in SCLC.

**DISCUSSION**

Here, we integrated our own omics data (transcriptome and regulome) and public omics data (genome and pharmacogenome) to elucidate the multi-omics integration-based prioritisation of ceRNA-mediated network characteristics, pathways and drug candidates in SCLC. The prioritisation of the SCLC ceRNA regulatory network consisted of two mRNAs (CSF3R/GAA), two miRNAs (hsa-miR-4525/hsa-miR-6747-3p), three lncRNAs (AC005005.4-201/DLX6-AS1-201/NEAT1-203) and two circRNAs (circRNA-hsa_HLA-B_1 and hsa_VEGFC_8). The expression levels of mRNAs, lncRNAs and circRNAs decreased in SCLC, while the expression levels of miRNAs increased in SCLC. In addition, lncRNAs (IncRNA-AC005005.4-201 and NEAT1-203) and circRNAs (circRNA-hsa_HLA-B_1 and hsa_VEGFC_8) may regulate the inhibited effects of hsa-miR-6747-3p for CSF3R expression in SCLC, and lncRNA-DLX6-AS1-201 or circRNA-hsa_HLA-B_1 may neutralise the negative regulation of hsa-miR-4525 related to GAA in SCLC. The pharmacogenomics analysis identified CSF3R and GAA as targets of FavId and Trastuzumab deruxtecan, respectively. The SCLC-associated pathway analysis revealed that CSF3R was involved in the autophagy pathway, while GAA was involved in the glucose metabolism pathway. These findings may contribute to understanding the molecular pathogenesis of SCLC, supporting the development of novel diagnostics and therapeutic compounds for SCLC patients in clinical settings.
### TABLE 4 | Functional enrichment analysis and pathway results of lncRNAs in the ceRNA network.

| ID          | Description                                    | Ontology | Bg Ratio | p value | Adjusted p |
|-------------|------------------------------------------------|----------|----------|---------|------------|
| GO:0050911 | Detection of chemical stimulus involved in sensory perception of smell | BP       | 0.0252   | 2.525E-19 | 1.549E-15 |
| GO:0032199 | Reverse transcription involved in RNA-mediated transposition | BP       | 0.0486   | 2.0772E-15 | 6.3707E-12 |
| GO:0090305 | Nucleic acid phosphodiester bond hydrolysis       | BP       | 0.058    | 2.5433E-14 | 5.2002E-11 |
| GO:0007186 | G-protein coupled receptor signalling pathway     | BP       | 0.0406   | 7.625E-13  | 1.1693E-09 |
| GO:0097252 | Oligodendrocyte apoptotic process                 | BP       | 0.039    | 1.6472E-11 | 2.0208E-06 |
| GO:0062798 | Nucleotide-excision repair                        | BP       | 0.0402   | 4.236E-11  | 4.3232E-08 |
| GO:0090200 | Positive regulation of release of cytochrome c from mitochondria | BP       | 0.0399   | 8.0612E-11 | 6.7949E-08 |
| GO:0007333 | DNA strand renaturation                          | BP       | 0.0395   | 8.8620E-11 | 6.7949E-08 |
| GO:007569  | Cell aging                                       | BP       | 0.0397   | 1.1273E-10 | 7.6831E-08 |
| GO:0030308 | Negative regulation of cell growth               | BP       | 0.0447   | 1.8945E-10 | 1.1621E-07 |
| GO:007275  | Multicellular organism development                | BP       | 0.0664   | 2.2891E-08 | 1.2765E-05 |
| GO:006310  | DNA recombination                                | BP       | 0.0325   | 3.6134E-08 | 1.8475E-05 |
| GO:0032197 | Transposition, RNA-mediated                      | BP       | 0.0081   | 6.9777E-06 | 3.0572E-03 |
| GO:0098987 | Cellular process                                 | BP       | 0.003    | 1.2086E-05 | 4.9352E-03 |
| GO:006259  | DNA metabolic process                            | BP       | 0.0064   | 1.4735E-05 | 6.6491E-03 |
| GO:007156  | Homophilic cell adhesion via plasma membrane adhesion molecules | BP       | 0.0098   | 7.3178E-05 | 2.6599E-02 |
| GO:0016043 | Cellular component organisation                   | BP       | 0.0064   | 7.8691E-05 | 2.6816E-02 |
| GO:0044238 | Primary metabolic process                        | BP       | 0.0027   | 1.3610E-04 | 4.3939E-02 |
| GO:0048741 | Skeletal muscle fibre development                | BP       | 0.0141   | 1.6591E-04 | 4.8714E-02 |
| GO:0033338 | Metanephros morphogenesis                        | BP       | 0.001    | 1.7472E-04 | 4.8714E-02 |
| GO:0070207 | Lens fibre cell development                      | CC       | 0.001    | 1.7472E-04 | 4.8714E-02 |
| GO:0044424 | Intracellular part                               | CC       | 0.007    | 1.7884E-07 | 1.6189E-04 |
| GO:0043229 | Intracellular organelle                          | CC       | 0.0019   | 1.2486E-06 | 4.2986E-04 |
| GO:0005886 | Plasma membrane                                  | CC       | 0.1378   | 1.4243E-06 | 4.2986E-04 |
| GO:0044446 | Intracellular organelle part                     | CC       | 0.0032   | 2.8382E-06 | 6.4257E-04 |
| GO:0098588 | Bounding membrane of organelle                   | CC       | 0.0086   | 5.0429E-05 | 9.1302E-03 |
| GO:0044456 | Synapse part                                     | CC       | 0.0013   | 1.3286E-05 | 9.921E-02  |
| GO:0005739 | Mitochondrion                                   | CC       | 0.0821   | 1.6615E-04 | 1.9921E-02 |
| GO:0005796 | Golgi lumen                                     | CC       | 0.0066   | 1.7604E-04 | 1.9921E-02 |
| GO:0005578 | Proteinaceous extracellular matrix               | CC       | 0.0098   | 2.3813E-04 | 2.3264E-02 |
| GO:0016021 | Integral component of membrane                   | CC       | 0.2479   | 2.5699E-04 | 2.3264E-02 |
| GO:0097546 | Ciliary base                                    | CC       | 0.0041   | 5.4612E-04 | 4.4944E-02 |
| GO:005887  | Integral component of plasma membrane            | CC       | 0.068    | 6.2753E-04 | 4.7340E-02 |
| GO:0039864 | RNA-directed DNA polymerase activity             | MF       | 0.0534   | 7.1861E-20 | 1.0143E-16 |
| GO:004984  | Olfactory receptor activity                      | MF       | 0.0249   | 1.0694E-19 | 1.0143E-16 |
| GO:0049301 | G-protein coupled receptor activity              | MF       | 0.0316   | 4.2156E-17 | 6.6491E-14 |
| GO:009036  | Type II site-specific deoxyribonuclease activity | MF       | 0.0479   | 1.2775E-16 | 6.0586E-14 |
| GO:005507  | Copper ion binding                              | MF       | 0.0408   | 1.0171E-10 | 6.3588E-08 |
| GO:005488  | Binding                                         | MF       | 0.0105   | 1.9986E-10 | 6.3171E-08 |
| GO:0043167 | Ion binding                                     | MF       | 0.0116   | 3.2373E-07 | 9.1428E-05 |
| GO:005549  | Odorant binding                                 | MF       | 0.0056   | 1.5499E-06 | 6.3752E-04 |
| hsa04740   | Olfactory transduction                          | KEGG     | 0.0589   | 8.091E-04  | 2.2399E-07 |
| hsa04915   | Neuroactive ligand-receptor interaction          | KEGG     | 0.0385   | 5.7920E-08 | 8.0173E-06 |
| hsa0533    | Nicotine addiction                              | KEGG     | 0.0054   | 2.1224E-04 | 1.9585E-02 |
| hsa04973   | Carbohydrate digestion and absorption           | KEGG     | 0.0076   | 5.8461E-04 | 3.3095E-02 |
| hsa04974   | Protein digestion and absorption                | KEGG     | 0.0102   | 5.9763E-04 | 3.3095E-02 |

GO, gene ontology; BP, biological process; CC, cellular component; KEGG, Kyoto Encyclopaedia of Genes and Genomes; ceRNA, competing endogenous RNA; circRNA, circular RNAs; lncRNA, long noncoding RNA; miRNA, microRNA; mRNA, messenger RNA; Bg, background.

### TABLE 5 | Functional enrichment analysis of circRNAs in the ceRNA network.

| ID          | Description                                    | Ontology | Bg Ratio | p value | Adjusted p |
|-------------|------------------------------------------------|----------|----------|---------|------------|
| GO:0032655 | regulation of interleukin-12 production        | BP       | 0.0001   | 2.963E-04 | 3.119E-04 |
| GO:0032675 | regulation of interleukin-6 production         | BP       | 0.0001   | 2.963E-04 | 3.119E-04 |
| GO:2001198 | regulation of dendritic cell differentiation    | BP       | 0.0001   | 2.963E-04 | 3.119E-04 |
| GO:0002667 | regulation of T cell anergy                    | BP       | 0.0002   | 8.888E-04 | 7.017E-04 |

(Continued)
| ID            | Description                                                                 | Ontology | Bg Ratio  | p value  | Adjusted p |
|---------------|-----------------------------------------------------------------------------|----------|-----------|----------|------------|
| GO:0002486    | antigen processing and presentation of endogenous peptide antigen via MHC class I via ER pathway, TAP-independent | BP       | 0.0004    | 1.481E-03| 8.311E-04  |
| GO:0015031    | protein transport                                                           | BP       | 0.0175    | 1.784E-03| 8.311E-04  |
| GO:0001916    | positive regulation of T cell–mediated cytotoxicity                        | BP       | 0.0005    | 2.073E-03| 8.311E-04  |
| GO:0016045    | detection of bacterium                                                       | BP       | 0.0006    | 2.369E-03| 8.311E-04  |
| GO:0042270    | protection from natural killer cell–mediated cytotoxicity                  | BP       | 0.0006    | 2.369E-03| 8.311E-04  |
| GO:0002480    | antigen processing and presentation of exogenous peptide antigen via MHC class I, TAP-independent | BP       | 0.0007    | 2.664E-03| 8.414E-04  |
| GO:0030100    | regulation of endocytosis                                                   | BP       | 0.0010    | 3.847E-03| 1.104E-03  |
| GO:0006904    | vesicle docking involved in exocytosis                                      | BP       | 0.0011    | 4.438E-03| 1.168E-03  |
| GO:0060337    | type I interferon signalling pathway                                         | BP       | 0.0022    | 8.861E-03| 2.152E-03  |
| GO:0002479    | antigen processing and presentation of exogenous peptide antigen via MHC class I, TAP-independent | BP       | 0.0030    | 1.180E-02| 2.546E-03  |
| GO:0060333    | interferon gamma–mediated signalling pathway                                | BP       | 0.0030    | 1.210E-02| 2.546E-03  |
| GO:0051726    | regulation of cell cycle                                                     | BP       | 0.0074    | 2.931E-02| 5.784E-03  |
| GO:0006367    | transcription initiation from RNA polymerase II promoter                    | BP       | 0.0106    | 4.257E-02| 7.908E-03  |
| GO:0006468    | protein phosphorylation                                                     | BP       | 0.0122    | 4.801E-02| 8.423E-03  |
| GO:0031901    | early endosome membrane                                                      | CC       | 0.0062    | 1.137E-04| 5.983E-04  |
| GO:0042612    | MHC class I protein complex                                                  | CC       | 0.0010    | 2.892E-03| 6.082E-03  |
| GO:0016592    | mediator complex                                                             | CC       | 0.0017    | 4.964E-03| 6.082E-03  |
| GO:0071556    | integral component of the luminal side of endoplasmic reticulum membrane    | CC       | 0.0017    | 4.964E-03| 6.082E-03  |
| GO:0012507    | ER to Golgi transport vesicle membrane                                       | CC       | 0.0019    | 5.778E-03| 6.082E-03  |
| GO:0030670    | phagocytic vesicle membrane                                                  | CC       | 0.0028    | 8.454E-03| 7.415E-03  |
| GO:0046977    | TAP binding                                                                  | MF       | 0.0004    | 1.098E-03| 3.107E-03  |
| GO:0008353    | RNA polymerase II carboxy-terminal domain kinase activity                    | MF       | 0.0007    | 1.967E-03| 3.107E-03  |
| GO:0004693    | cyclin-dependent protein serine/threonine kinase activity                    | MF       | 0.0020    | 6.113E-03| 5.857E-03  |
| GO:0042605    | peptide antigen binding                                                     | MF       | 0.0025    | 7.419E-03| 5.857E-03  |
| GO:0051087    | chaperone binding                                                            | MF       | 0.0039    | 1.155E-02| 6.307E-03  |
| GO:0008565    | protein transporter activity                                                 | MF       | 0.0040    | 1.198E-02| 6.307E-03  |
| GO:0008289    | lipid binding                                                                | MF       | 0.0061    | 1.826E-02| 8.239E-03  |
| GO:0005102    | receptor binding                                                             | MF       | 0.0102    | 3.031E-02| 1.197E-02  |

GO, gene ontology; BP, biological process; CC, cellular component; ceRNA, competing endogenous RNA; circRNA, circular RNAs; Bg, background.
## TABLE 6 | Functional enrichment analysis of miRNAs in the ceRNA network.

| ID          | Description                                               | Ontology / Description | Bg Ratio | p value | Adjusted p |
|-------------|-----------------------------------------------------------|------------------------|----------|---------|------------|
| GO:0006355  | regulation of transcription, DNA-templated               | BP                     | 0.0921   | 8.5782E-11 | 5.7934E-07 |
| GO:0000122  | negative regulation of transcription from RNA polymerase II promoter | BP                     | 0.0565   | 1.5250E-05 | 5.1498E-05 |
| GO:0045944  | positive regulation of transcription from RNA polymerase II promoter | BP                     | 0.0664   | 2.6517E-08 | 9.6966E-05 |
| GO:0060348  | bone development                                          | BP                     | 0.0174   | 6.6166E-08 | 1.0284E-04 |
| GO:0017144  | drug metabolic process                                    | BP                     | 0.0187   | 8.6063E-08 | 1.0284E-04 |
| GO:0017187  | peptidyl-glutamic acid carboxylation                      | BP                     | 0.0179   | 9.1359E-08 | 1.0284E-04 |
| GO:0042373  | vitamin K metabolic process                               | BP                     | 0.0177   | 2.6291E-07 | 2.5366E-04 |
| GO:0007250  | activation of NF-kappa-inducing kinase activity           | BP                     | 0.0124   | 3.1140E-07 | 2.5645E-04 |
| GO:0007156  | hemophilic cell adhesion via plasma membrane adhesion molecules | BP                     | 0.0098   | 3.4174E-07 | 2.5645E-04 |
| GO:0032743  | positive regulation of interleukin 2 production           | BP                     | 0.0125   | 6.9433E-07 | 4.6893E-04 |
| GO:2000679  | positive regulation of transcription regulatory region DNA binding | BP                     | 0.017   | 1.4950E-06 | 9.1787E-04 |
| GO:0031293  | membrane protein intracellular domain proteolysis         | BP                     | 0.0124   | 2.1666E-06 | 1.2306E-03 |
| GO:0002756  | MyD88-independent toll-like receptor signalling pathway   | BP                     | 0.0116   | 3.2308E-06 | 1.6785E-03 |
| GO:0000187  | activation of MAPK activity                               | BP                     | 0.0213   | 5.9088E-06 | 2.8504E-03 |
| GO:0002726  | positive regulation of T cell cytokine production         | BP                     | 0.0124   | 9.3027E-06 | 4.1885E-03 |
| GO:0070555  | response to interleukin 1                                 | BP                     | 0.0998   | 1.0189E-05 | 4.2601E-03 |
| GO:0051865  | protein auto-ubiquitination                               | BP                     | 0.0143   | 1.0723E-05 | 4.2601E-03 |
| GO:0045672  | positive regulation of osteoclast differentiation          | BP                     | 0.0125   | 1.3074E-05 | 4.7509E-03 |
| GO:0001932  | regulation of protein phosphorylation                     | BP                     | 0.003    | 1.4090E-05 | 4.7509E-03 |
| GO:0070534  | protein K63-linked ubiquitination                         | BP                     | 0.0182   | 1.4069E-05 | 4.7509E-03 |
| GO:0031398  | positive regulation of protein ubiquitination             | BP                     | 0.0121   | 2.6984E-05 | 8.2836E-03 |
| GO:0034162  | toll-like receptor 9 signalling pathway                    | BP                     | 0.0121   | 2.6984E-05 | 8.2836E-03 |
| GO:0070423  | nucleotide-binding oligomerisation domain containing signalling pathway | BP                     | 0.0175  | 2.8472E-05 | 8.3605E-03 |
| GO:0043507  | positive regulation of JUN kinase activity                | BP                     | 0.0139   | 4.0466E-05 | 1.1386E-02 |
| GO:0030574  | collagen catabolic process                                | BP                     | 0.0023   | 4.2766E-05 | 1.1553E-02 |
| GO:0071222  | cellular response to lipopolysaccharide                    | BP                     | 0.0118   | 5.4294E-05 | 1.4070E-02 |
| GO:0002755  | MyD88-dependent toll-like receptor signalling pathway     | BP                     | 0.0181   | 5.6249E-05 | 1.4070E-02 |
| GO:0046513  | ceramide biosynthetic process                             | BP                     | 0.0096   | 6.7342E-05 | 1.6134E-02 |
| GO:0035019  | somatic stem cell population maintenance                  | BP                     | 0.0075   | 6.9279E-05 | 1.6134E-02 |
| GO:0001752  | mesoderm formation                                        | BP                     | 0.0013   | 8.3053E-05 | 1.8397E-02 |
| GO:0007506  | blood coagulation                                         | BP                     | 0.0236   | 9.1112E-05 | 1.9850E-02 |

(Continued)
TABLE 6 | Continued

| ID          | Description                                                      | Ontology | Bg Ratio | p value | Adjusted p |
|-------------|------------------------------------------------------------------|----------|----------|---------|------------|
| GO:0050870  | positive regulation of T cell activation                         | BP       | 0.0067   | 1.5077E-04 | 3.1820E-02 |
| GO:0007155  | cell adhesion                                                    | BP       | 0.0111   | 1.5634E-04 | 3.1997E-02 |
| GO:0015886  | heme transport                                                   | BP       | 0.0035   | 1.6785E-04 | 3.2879E-02 |
| GO:0043065  | positive regulation of apoptotic process                         | BP       | 0.028    | 1.7039E-04 | 3.2879E-02 |
| GO:0045059  | positive thymic T cell selection                                 | BP       | 0.0023   | 1.9247E-04 | 3.6108E-02 |
| GO:0035023  | regulation of Rho protein signal transduction                    | BP       | 0.0039   | 2.1384E-04 | 3.9032E-02 |
| GO:0051092  | positive regulation of NF-kappa B transcription factor activity  | BP       | 0.026    | 2.2701E-04 | 4.0346E-02 |
| GO:0031410  | cytoplasmic vesicle                                              | CC       | 0.014    | 8.1251E-07 | 6.2029E-04 |
| GO:0005789  | endoplasmic reticulum membrane                                   | CC       | 0.0602   | 1.2645E-06 | 6.2029E-04 |
| GO:0010008  | endosome membrane                                                | CC       | 0.0227   | 1.8113E-06 | 6.2029E-04 |
| GO:0005829  | cytosol                                                          | CC       | 0.1935   | 7.5017E-06 | 1.9267E-03 |
| GO:0034704  | calcium channel complex                                           | CC       | 0.0008   | 5.8805E-05 | 1.2083E-02 |
| GO:0005811  | lipid droplet                                                    | CC       | 0.012    | 7.5151E-05 | 1.2888E-02 |
| GO:0035631  | CD40 receptor complex                                             | CC       | 0.0098   | 1.0108E-04 | 1.3848E-02 |
| GO:0009898  | cytoplasmic side of plasma membrane                              | CC       | 0.0116   | 1.0738E-04 | 1.3848E-02 |
| GO:0005667  | transcription factor complex                                      | CC       | 0.0095   | 3.8115E-04 | 4.3509E-02 |
| GO:0003700  | transcription factor activity, sequence-specific DNA binding      | MF       | 0.0684   | 1.2784E-14 | 2.7816E-11 |
| GO:0009977  | RNA polymerase II regulatory region sequence-specific DNA binding | MF       | 0.0261   | 6.2083E-13 | 6.7593E-10 |
| GO:0046872  | metal ion binding                                                | MF       | 0.1355   | 1.8538E-08 | 1.3445E-05 |
| GO:0031996  | thioesterase binding                                             | MF       | 0.0128   | 1.6534E-07 | 7.5276E-05 |
| GO:0031624  | ubiquitin conjugating enzyme binding                              | MF       | 0.0136   | 1.7299E-07 | 7.5276E-05 |
| GO:0042826  | histone deacetylase binding                                       | MF       | 0.0191   | 3.5880E-07 | 1.3011E-04 |
| GO:0047057  | vitamin-K-epoxide reductase (warfarin-sensitive) activity        | MF       | 0.0174   | 4.3664E-07 | 1.3572E-04 |
| GO:0043422  | protein kinase B binding                                          | MF       | 0.0122   | 5.3369E-07 | 1.4515E-04 |
| GO:0031435  | mitogen-activated protein kinase binding                          | MF       | 0.0125   | 2.4616E-06 | 5.9505E-04 |
| GO:0005164  | tumour necrosis factor receptor binding                           | MF       | 0.0133   | 4.8342E-06 | 1.0518E-03 |
| GO:0050291  | sphingosine N-acyltransferase activity                            | MF       | 0.0083   | 2.3602E-05 | 4.6685E-03 |
| GO:0003682  | chromatin binding                                                | MF       | 0.0168   | 3.5302E-05 | 6.4008E-03 |
| GO:0001077  | transcriptional activator activity, RNA polymerase II core promoter proximal region sequence-specific binding | MF       | 0.0219   | 4.3610E-05 | 7.2989E-03 |
| GO:0005096  | GTPase activator activity                                         | MF       | 0.0123   | 1.0248E-04 | 1.5927E-02 |
| GO:0031625  | ubiquitin protein ligase binding                                  | MF       | 0.0317   | 1.2898E-04 | 1.8708E-02 |

(Continued)
### TABLE 6 | Continued

| ID             | Description                                                                 | Ontology | Bg Ratio | p value       | Adjusted p       |
|----------------|------------------------------------------------------------------------------|----------|----------|---------------|------------------|
| GO:0001078     | transcriptional repressor activity, RNA polymerase II core promoter proximal region sequence-specific binding | MF       | 0.009    | 1.5448E-04    | 2.1007E-02       |
| GO:0000978     | RNA polymerase II core promoter proximal region sequence-specific DNA binding | MF       | 0.0242   | 1.9703E-04    | 2.5217E-02       |
| GO:0008270     | zinc ion binding                                                             | MF       | 0.0638   | 2.6201E-04    | 3.1672E-02       |
| GO:0001047     | core promoter binding                                                        | MF       | 0.0109   | 4.3480E-04    | 4.9792E-02       |

GO, gene ontology; BP, biological process; CC, cellular component; ceRNA, competing endogenous RNA; miRNA, microRNA; Bg, background.

### TABLE 7 | Pathway results of miRNAs in the ceRNA network.

| ID             | Description                               | Bg Ratio | p value       | Adjusted p       |
|----------------|-------------------------------------------|----------|---------------|------------------|
| hsa04921       | Oxytocin signalling pathway               | 0.0212   | 1.3323E-08    | 2.9190E-06       |
| hsa04261       | Adrenergic signalling in cardiomyocytes   | 0.0208   | 6.2595E-07    | 6.5092E-05       |
| hsa04024       | cAMP signalling pathway                   | 0.0273   | 8.9189E-07    | 6.5092E-05       |
| hsa04510       | Focal adhesion                            | 0.0298   | 1.5422E-05    | 7.4010E-04       |
| hsa04750       | Inflammatory mediator regulation of TRP channels | 0.0137 | 1.6901E-05    | 7.4010E-04       |
| hsa04713       | Circadian entrainment                     | 0.0125   | 2.1580E-05    | 7.8748E-04       |
| hsa04360       | Axon guidance                             | 0.0239   | 2.5931E-05    | 8.1108E-04       |
| hsa04015       | Rap1 signalling pathway                   | 0.03     | 4.7767E-05    | 1.3073E-03       |
| hsa05200       | Pathways in cancer                        | 0.055    | 6.2554E-05    | 1.5218E-03       |
| hsa04611       | Platelet activation                       | 0.0165   | 7.0689E-05    | 1.5477E-03       |
| hsa04010       | MAPK signalling pathway                   | 0.0381   | 1.1422E-04    | 2.2735E-03       |
| hsa04724       | Glutamatergic synapse                     | 0.0149   | 1.3881E-04    | 2.3601E-03       |
| hsa04725       | Cholinergic synapse                       | 0.0151   | 1.4013E-04    | 2.3601E-03       |
| hsa05206       | MicroRNAs in cancer                      | 0.0193   | 2.6751E-04    | 4.1690E-03       |
| hsa04728       | Dopaminergic synapse                      | 0.0165   | 2.8562E-04    | 4.1690E-03       |
| hsa04925       | Aldosterone synthesis and secretion       | 0.0108   | 3.4051E-04    | 4.6598E-03       |
| hsa01522       | Endocrine resistance                     | 0.0132   | 3.9237E-04    | 4.6724E-03       |
| hsa04722       | Neurotrophin signalling pathway           | 0.0168   | 3.9400E-04    | 4.6724E-03       |
| hsa04720       | Long-term potentiation                    | 0.0089   | 4.0547E-04    | 4.6724E-03       |
| hsa04390       | Hippo signalling pathway                  | 0.0209   | 4.5090E-04    | 4.9362E-03       |
| hsa04512       | ECM–receptor interaction                 | 0.0112   | 5.2201E-04    | 5.4425E-03       |
| hsa04512       | Wnt signalling pathway                    | 0.0195   | 6.5195E-04    | 6.4883E-03       |
| hsa04915       | Oestrogen signalling pathway              | 0.0137   | 7.9656E-04    | 7.5828E-03       |

(Continued)
| ID    | Description                                      | Bg Ratio | p value     | Adjusted p |
|-------|--------------------------------------------------|----------|-------------|------------|
| hsa04924 | Renin secretion                                 | 0.0086   | 9.2945E-04  | 8.4792E-03 |
| hsa04022 | cGMP-PKG signalling pathway                      | 0.0247   | 1.2704E-03  | 1.1126E-02 |
| hsa04923 | Regulation of lipolysis in adipocytes            | 0.0082   | 1.3531E-03  | 1.1192E-02 |
| hsa05210 | Colorectal cancer                                | 0.009    | 1.4528E-03  | 1.1192E-02 |
| hsa04014 | Ras signalling pathway                           | 0.0325   | 1.4684E-03  | 1.1192E-02 |
| hsa04912 | GnRH signalling pathway                          | 0.0124   | 1.5787E-03  | 1.1192E-02 |
| hsa04727 | GABAergic synapse                                 | 0.0114   | 1.5828E-03  | 1.1192E-02 |
| hsa04911 | Insulin secretion                                | 0.0116   | 1.5946E-03  | 1.1192E-02 |
| hsa00512 | Mucin type O-Glycan biosynthesis                 | 0.0039   | 2.0450E-03  | 1.3992E-02 |
| hsa04910 | Insulin signalling pathway                        | 0.0212   | 2.0974E-03  | 1.4661E-02 |
| hsa00514 | Other types of O-glycan biosynthesis             | 0.0042   | 2.3096E-03  | 1.4862E-02 |
| hsa04012 | ErbB signalling pathway                          | 0.0121   | 3.0528E-03  | 1.8829E-02 |
| hsa04270 | Vascular smooth muscle contraction               | 0.017    | 3.0960E-03  | 1.8829E-02 |
| hsa01212 | Fatty acid metabolism                            | 0.0068   | 4.0784E-03  | 2.3933E-02 |
| hsa04020 | Calcium signalling pathway                        | 0.0302   | 4.2385E-03  | 2.3933E-02 |
| hsa04930 | Type II diabetes mellitus                         | 0.0081   | 4.4096E-03  | 2.3933E-02 |
| hsa04931 | Insulin resistance                               | 0.0158   | 4.4262E-03  | 2.3933E-02 |
| hsa04971 | Gastric acid secretion                           | 0.0097   | 4.4817E-03  | 2.3933E-02 |
| hsa04152 | AMPK signalling pathway                           | 0.018    | 4.7769E-03  | 2.4802E-02 |
| hsa04211 | Longevity regulating pathway                     | 0.0135   | 5.2272E-03  | 2.6447E-02 |
| hsa04916 | Melanogenesis                                    | 0.0132   | 5.3149E-03  | 2.6447E-02 |
| hsa04340 | Hedgehog signalling pathway                      | 0.0069   | 6.1584E-03  | 2.9698E-02 |
| hsa04213 | Longevity regulating pathway – multiple species   | 0.009    | 6.3540E-03  | 2.9698E-02 |
| hsa05221 | Acute myeloid leukaemia                          | 0.0082   | 6.3751E-03  | 2.9698E-02 |
| hsa04550 | Signalling pathways regulating pluripotency of stem cells | 0.0196 | 6.6773E-03  | 3.0458E-02 |
| hsa05410 | Hypertrophic cardiomyopathy (HCM)                | 0.0115   | 7.8953E-03  | 3.5279E-02 |
| hsa05412 | Arrhythmogenic right ventricular cardiomyopathy (ARVC) | 0.0097 | 8.6718E-03  | 3.7274E-02 |
| hsa04962 | Vasopressin-regulated water reabsorption          | 0.006    | 8.6824E-03  | 3.7274E-02 |
| hsa04144 | Endocytosis                                      | 0.0376   | 9.4078E-03  | 3.9612E-02 |
| hsa04068 | FoxO signalling pathway                          | 0.0201   | 9.9201E-03  | 4.0816E-02 |
| hsa04350 | TGF-beta signalling pathway                      | 0.0119   | 1.0253E-02  | 4.0816E-02 |

(Continued)
In this study, we first reported the multi-omics integration-based prioritisation of the lncRNA/circRNA-miRNA-mRNA ceRNA disease network, as well as the molecular characteristics and drug candidates or repurposed drugs in SCLC. The ceRNA is a layer of gene regulation in diseases, and the transcripts can regulate each other at the post-transcription level by competing for shared miRNAs (12, 16, 17). Here, we found that two lncRNAs (lncRNA-AC005005.4-201 and NEAT1-203) and two circRNAs (circRNA-hsa_HLA-B_1 and hsa_VEGFC_8) may regulate the inhibiting effects of hsa-miR-6747-3p for CSF3R expression, while lncRNA-DLX6-AS1-201 or circRNA-hsa_HLA-B_1 may neutralise the negative regulation of hsa-

**TABLE 7 | Continued**

| ID     | Description                        | Bg Ratio | p value     | Adjusted p   |
|--------|------------------------------------|----------|-------------|--------------|
| hsa05222 | Small cell lung cancer             | 0.0119   | 1.0253E-02  | 4.0816E-02   |
| hsa01521 | EGFR tyrosine kinase inhibitor resistance | 0.0116   | 1.0447E-02  | 4.0847E-02   |
| hsa00531 | Glycosaminoglycan degradation       | 0.0026   | 1.1704E-02  | 4.4958E-02   |
| hsa04723 | Retrograde endocannabinoid signalling | 0.0133   | 1.1967E-02  | 4.5173E-02   |
| hsa04142 | Lysosome                           | 0.0175   | 1.2975E-02  | 4.8149E-02   |

KEGG, Kyoto Encyclopaedia of Genes and Genomes; ceRNA, competing endogenous RNA; miRNA, microRNA; Bg, background.

**TABLE 8 | Potential drug candidates of mRNAs in the ceRNA networks in SCLC.**

| mRNAs                               | Drug candidate | Type*                  | Therapy*                  | Main roles*                                                                 | Data resource                                      |
|-------------------------------------|----------------|------------------------|---------------------------|----------------------------------------------------------------------------|---------------------------------------------------|
| Colony-stimulating factor 3 receptor (CSF3R) | FavIid          | an active immunotherapy | Tumour therapy            | based upon unique genetic information extracted from a patient’s tumour     | https://go.drugbank.com/drugs/DB05249              |
|                                     | Pegfilgrastim    | a recombinant human granulocyte colony stimulating factor | Adjuvant therapy          | stimulate the production of neutrophils and prevent febrile neutropenia or infections after myelosuppressive chemotherapy | https://go.drugbank.com/drugs/DB00019              |
|                                     | Filgrastim       | a form of recombinant human granulocyte colony stimulating factor | Adjuvant therapy          | induce the production of granulocytes and lower infection risk after myelosuppressive therapy | https://go.drugbank.com/drugs/DB00099              |
|                                     | Lenograstim      | a granulocyte colony-stimulating factor | Adjuvant therapy          | reduce the duration of neutropenia in bone marrow transplant and cytotoxic chemotherapy, as well as mobilizing hematopoietic stem cells in healthy donors | https://go.drugbank.com/drugs/DB13144              |
|                                     | Lipegfilgrastim  | a medication            | Adjuvant therapy          | reduce the duration of chemotherapy-induced neutropenia and incidence of febrile neutropenia in cytotoxic chemotherapy | https://go.drugbank.com/drugs/DB13200              |
| Acid alpha-glucosidase (GAA)         | Trastuzumab deruxtecan | an antibody             | Tumour therapy            | treat certain types of unrectable or metastatic HER-2 positive breast cancer | https://go.drugbank.com/drugs/DB14962              |
|                                     | Acarbose         | an alpha-glucosidase inhibitor | Other therapy             | adjunctly with diet and exercise for the management of glycaemic control in patients with type 2 diabetes mellitus. | https://go.drugbank.com/drugs/DB00284              |
|                                     | AT2220           | pharmacological chaperones | Other therapy             | increase GAA activity in cell lines derived from Pompe patients and in transfected cells expressing misfolded forms of GAA | https://go.drugbank.com/drugs/DB05200              |
|                                     | Miglitol         | an oral alpha-glucosidase inhibitor | Other therapy             | improve glycaemic control by delaying the digestion of carbohydrates       | https://go.drugbank.com/drugs/DB00491              |
| FGR Proto-Oncogene, Src Family Tyrosine Kinase (FGR) | Dasatinib       | a tyrosine kinase inhibito | Tumour therapy            | treat lymphoblastic or chronic myeloid leukemia with resistance or intolerance to prior therapy | https://go.drugbank.com/drugs/DB01254              |
|                                     | Zanubrutinib     | a kinase inhibitor       | Tumour therapy            | treat mantle cell lymphoma, a type of B-cell non-Hodgkin lymphoma, in adults who previously received therapy. | https://go.drugbank.com/drugs/DB15035              |
|                                     | Fostamatinib     | a spleen tyrosine kinase inhibitor | Other therapy             | treat chronic immune thrombocytopenia after attempting one other treatment. | https://go.drugbank.com/drugs/DB12010              |

ceRNA, competing endogenous RNA; SCLC, small cell lung cancer; HER-2, human epidermal growth factor receptor-2; *, the information is from Drugbank (https://go.drugbank.com/).
miR-4525 for GAA. Consistent with our findings for dysregulated lncRNAs in SCLC, previous studies found that lncRNAs DLX6-AS1 and NEAT1 were significantly dysregulated in non-SCLC, gastric cancer and pancreatic cancer (59–62). Specifically, upregulated DLX6-AS1 in gastric cancer tissue associated with distant metastasis and a poor clinical prognosis, while siRNA-DLX6-AS1 may inhibit gastric cancer cell proliferation, migration, invasion and the epithelial-mesenchymal transition in vitro (18). In addition, our study identified the regulatory axis in lncRNA-DLX6-AS1-201/hsa-miR-4525/GAA, which associated with the glucose metabolism pathway in SCLC. Interestingly, Qian et al. reported that sh-DLX6-AS1 may modulate glucose metabolism and cell growth via miR-4290/3-phosphoinositide-dependent protein kinase 1 in gastric cancer cells (63). Considering the role of DLX6-AS1 in glucose metabolism, we inferred that DLX6-AS1 could affect the occurrence and progression of SCLC via glucose metabolism through modulating hsa-miR-4525/GAA in SCLC. Similar to the

### Table 9 | Pathways of mRNAs in the ceRNA networks in SCLC.

| mRNAs                                      | Gene ontology (GO) based on molecular function | Pathways                        | Associated to SCLC pathway     |
|---------------------------------------------|-----------------------------------------------|---------------------------------|--------------------------------|
| Colony-stimulating factor 3 receptor (CSF3R)| Cytokine binding (GO:0019955)                 | Autophagy pathway               | Güngör E, et al. (66); Liu H, et al. (67) |
|                                             | Cytokine receptor activity (GO:004896)        | Akt signalling                  | na                             |
|                                             | Protein binding (GO:0049515)                  | PEDF-induced signalling         | na                             |
|                                             | Signalling receptor activity (GO:0038023)     | Cytokine signalling in the immune system | na                         |
|                                             | Granulocyte colony-stimulating factor binding (GO:0051916) | Hematopoietic cell lineage     | na                             |
|                                             | Catalytic activity (GO:003824)                | Glucose metabolism              | Yan X, et al. (58)            |
| Acid alpha-glucosidase (GAA)                | Hydrolyase activity, hydrolyzing O-glycosyl compounds (GO:0004553) | Innate immune system           | na                             |
|                                             | Alpha-1,4-glucosidase activity (GO:004558)   | Galactose metabolism            | na                             |
|                                             | Hydrolyase activity, acting on glycosid bonds (GO:004798) | Metabolism                    | na                             |
|                                             | Nucleotide binding (GO:000166)                | Innate immune system            | na                             |
| FGR Proto-Oncogene, Src Family Tyrosine Kinase (FGR) | Phosphotyrosine residue binding (GO:0001784) | Platelet homeostasis            | na                             |
|                                             | Protein kinase activity (GO:004672)           | Tyrosine kinases/adaptors       | na                             |
|                                             | Protein tyrosine kinase activity (GO:004713)  | CCR5 pathway in macrophages     | na                             |
|                                             | Transmembrane receptor tyrosine kinase activity (GO:004714) | Integrin pathway              | na                             |

ceRNA, competing endogenous RNA; SCLC, small cell lung cancer; Akt, protein kinase B; CCR5, chemokine-CC motif-receptor-5; GO, gene ontology; PEDF, pigment epithelium derived factor; na, not available.

### Figure 5 | Illustration of multi-omics–based prioritisation of the ceRNA subnetwork, drug candidates and pathways.

ATP, adenosine triphosphatase; AMPK, AMP-activated protein kinase; BCAAs, branched-chain amino acids; CoA, coenzyme A; ceRNA, competitive endogenous RNA; circRNA, circular RNA; CSF3R, colony-stimulating factor 3 receptor; GAA, acid alpha-glucosidase; IncRNA, long noncoding RNA; miRNA, microRNA; mRNA, messenger RNA; SCLC, small cell lung cancer; TCA, tricarboxylic acid.
other dysregulated lncRNA reports (59–62), Xu et al. found that lncRNA-NEAT1 may promote gastric cancer angiogenesis by enhancing the proliferation, migration and tube formation ability of endothelial cells through the miR-17-5p-transforming growth factor-β receptor 2 (TGFBR2) pathway (61), while lncRNA-NEAT1 may play a vital role in tumorigenesis and the development of SCLC through the hsa-miR-6747-3p/CSF3R axis. Importantly, in addition to lncRNA-DLX6-AS1 and NEAT1, we are the first to report another potential regulatory axis of ceRNA, while the regulatory mechanisms require further exploration through in vivo and in vitro studies. Our findings, however, suggest that the promising lncRNA/circRNA-miRNA-mRNA ceRNA regulatory characteristics in SCLC may provide new potential mechanisms and therapeutic targets.

To the best of our knowledge, this is also the first study to investigate the roles of CSF3R and GAA in the SCLC ceRNA regulation networks, pathways and drug candidates. CSF3R is a type 1 cytokine receptor, encoding the receptor for granulocyte colony-stimulating factor (G-CSF) and playing a crucial role in granulocyte proliferation and differentiation (64, 65). The altered CSF3R expression or activating heterozygous variants in CSF3R have been identified as risk factors in the development of multiple malignancies, such as colorectal cancer, myeloid malignancies and lymphoid malignancies (65–67). This is particularly the case for mutations in CSF3R commonly present in chronic neutrophilic leukaemia or atypical chronic myeloid leukaemia (68). Given the roles of CSF3R reported in chronic neutrophilic leukaemia or atypical chronic myeloid leukaemia (66, 68), our findings suggest that CSF3R might play a pivotal role in the occurrence and development of SCLC. Furthermore, our results suggest that CSF3R might modulate the autophagy pathway, which associated with SCLC (57, 58). The functions of autophagy in cancer may involve an anticancer or a cancer effect (69). Previous studies suggested that a hypoxia-HIF1A–AS2-autophagy interaction may play a role in drug sensitivity in SCLC, while a high expression of secreted phosphoprotein 1 (SPP1) inhibited autophagy and apoptosis, promoting the development of SCLC (57, 58). In addition, Rupniewska et al. found that SCLC cells may be more sensitive to autophagy inhibitors (70). In our study, CSF3R was identified as the potential drug target of Favld. Favld is an active immunotherapy with stimulating tumour-specific T cells and humoral immunity (71, 72). Alissafi et al. reported that autophagy-deficient therapy exhibited a mediated suppression of antitumour immunity via the efficient activation of tumour-specific CD4+ T cells (73), which was consistent with the mechanism of Favld in a tumour. Thus, our results suggest that genetic alterations or an altered expression of CSF3R may serve as a risk factor in SCLC development and associate with the autophagy pathway, while Favld could serve as a potential drug therapy through the CSF3R target to treat SCLC, even though additional in vivo or in vitro studies are needed to clarify these associations in SCLC. GAA, as one of the lysosomal enzymes, was the other key gene in our study. This is the first study to find that GAA might participate in the occurrence and development of SCLC via glucose metabolism. Similarly, Hamura et al. reported that the modulation of GAA could affect cell proliferation and apoptosis and manipulate chemoresistance in pancreatic cancer cells via dysfunctional mitochondria (74). The dysregulated metabolism of glucose in mitochondria is known as an adverse microenvironment in solid tumours, referred to as the Warburg effect, including glucose deprivation and lactic acidosis, potentially resulting in an elevated glycolytic activity in tumour cells (75–78). Yan et al. showed that glucose metabolic reprogramming improves SCLC cell proliferation and metastasis, suggesting it could be a potential regulatory strategy interfering with glucose metabolism in SCLC (56). Considering the function of GAA, which catalyses the production of glucose from glycogen in lysosomes, altering the GAA expression or genetic status could inhibit tumorigenesis in SCLC through the lysosome pathway (56, 74–78). Interestingly, the DrugBank analysis showed that the drug targeting GAA was Trastuzumab-deruxtecan. Trastuzumab-deruxtecan is primarily used for patients with human epidermal growth factor receptor 2 (HER2)–mutant tumours including non-SCLC and in the absence of SCLC (79–81). Upon binding to HER2, Trastuzumab-deruxtecan disrupts the HER2 signalling, undergoes internalisation and intracellular linker cleavage by lysosomal enzymes and ultimately causes DNA damage and apoptotic cell death (80). In addition, Martinho et al. found that the inhibitors of the HER family (mainly HER2) reduced cervical cancer aggressiveness by blocking glucose metabolism (82). Combined with the roles of the glucose metabolism pathway in SCLC and the antitumour roles of Trastuzumab-deruxtecan via the glucose metabolism pathway, our findings suggest that Trastuzumab-deruxtecan may be a promising drug candidate via GAA in SCLC through the glucose metabolism pathway. However, further in vivo or in vitro studies are needed to clarify these promising drug candidates’ ability to treat SCLC.

The strength of this study is our use of network-based multi-omics integration to prioritise ceRNA characteristics and drug candidates in SCLC from two well-characterised study cohorts, including newly tested whole-transcriptome sequencing data in the SCLC study, and the data were uploaded to a public platform [the Sequence Read Archive (SRA) database]. In addition to these strengths, we also note several limitations. First, our study included our own omics data and public data. In addition, the relatively small size of our cohort represents a limitation to our findings, although the results of the mRNA study were validated in a relatively large cohort. Second, the ceRNA characteristics and drug candidates and repurposing are quite promising, although further mechanistic studies from cells and animal models, as well as clinical validation studies, are needed. In addition, we performed no survival analysis in this study, since no available and suitable survival data were obtained from public databases, including the Cancer Genome Atlas (TCGA) and Kaplan–Meier plotter databases. Finally, the survival data in our SCLC plasma cohort were incapable of producing useful results for the prognostic analysis given the relatively small sample sizes and quite limited follow-up time.

In conclusion, we report primary findings related to a multi-omics integration-based prioritisation of the lncRNA/circRNA-
miRNA-mRNA ceRNA regulatory network, pathways and promising drug candidates in SCLC. These findings indicate novel, potential diagnostic and therapeutic targets in SCLC.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/Supplementary Material.

ETHICS STATEMENT

This study received ethical approval from the Ethics Committee of the Gansu Provincial Hospital, China (27 July 2020, No. 2020-183). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

W-DH, MZ, X-JW and JG contributed to the design of the study. X-JW and W-DH performed the sample collection, analysis and downloaded the data. X-JW and JG contributed to the data analysis and to writing the manuscript. W-DH, MZ, QY, X-JW and JG revised the manuscript. All authors approved the final version of the manuscript.

FUNDING

This study was supported by the Science–Technology Foundation for Young Scientist of the Gansu Province of China (Grant no.18JR3RA059), the Science–Technology Foundation for Scientists of the Gansu Province of China (Grant no.21JR7RA595), the Science–Technology Foundation for Lanzhou City of China (Grant no.2018-4-65) and the Scientists Fund of the Gansu Provincial Hospital of China (Grant no.18GSS4-25). Jing Gao was also supported by the Swedish Heart–Lung Foundation, the Swedish Asthma and Allergy Foundation, the Sigrid Jusélius Foundation and the Väinö and Laina Kivi Foundation.

ACKNOWLEDGMENTS

We extend our deepest gratitude to all of the patients who volunteered to participate in our study. We thank Jin Li, from the Faculty of Information Technology and Communication Sciences, Tampere University (Finland), for assistance with the tables and figures. We also extend our gratitude to Vanessa L Fuller, from Language Services at the University of Helsinki (Finland), for assistance with the initial English-language revision of this manuscript. In addition, we thank the Biomarker Technologies Corporation (Beijing, China) for sequencing technology and support. Figures were created using the BioRender software (@biorender.com).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.904865/full#supplementary-material.

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