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CDK1 and CCNA2 play important roles in oral squamous cell carcinoma

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Abstract

Oral squamous cell carcinoma (OSCC) is a malignant tumor that occurs in oral cavity and is dominated by squamous cells. The relationship between CDK1, CCNA2, and OSCC is still unclear. The OSCC datasets GSE74530 and GSE85195 configuration files were downloaded from the Gene Expression Omnibus (GEO) database and were derived from platforms GPL570 and GPL6480. Differentially expressed genes (DEGs) were screened. The weighted gene co-expression network analysis, functional enrichment analysis, gene set enrichment analysis, construction and analysis of protein–protein interaction (PPI) network, Comparative Toxicogenomics Database analysis were performed. Gene expression heatmap was drawn. TargetScan was used to screen miRNAs that regulate central DEGs. A total of 1756 DEGs were identified. According to Gene Ontology (GO) analysis, they were predominantly enriched in processes related to organic acid catabolic metabolism, centromeric, and chromosomal region condensation, and oxidoreductase activity. In Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis, the DEGs were mainly concentrated in metabolic pathways, P53 signaling pathway, and PPAR signaling pathway. Weighted gene co-expression network analysis was performed with a soft-thresholding power set at 9, leading to the identification of 6 core genes (BUB1B, CCNB1, KIF20A, CCNA2, CDCA8, CDK1). The gene expression heatmap revealed that core genes (CDK1, CCNA2) were highly expressed in OSCC samples. Comparative Toxicogenomics Database analysis demonstrated associations between the 6 genes (BUB1B, CCNB1, KIF20A, CCNA2, CDCA8, CDK1) and oral tumors, precancerous lesions, inflammation, immune system disorders, and tongue tumors. The associated miRNAs for CDK1 gene were hsa-miR-203a-3p.2, while for CCNA2 gene, they were hsa-miR-6766-3p, hsa-miR-4782-3p, and hsa-miR-219a-5p. CDK1 and CCNA2 are highly expressed in OSCC. The higher the expression of CDK1 and CCNA2, the worse the prognosis.

Abbreviations: CCNA2 = cell cyclin A2, CDK1 = Cyclin-Dependent Kinase 1, CTD = Comparative Toxicogenomics Database, DEGs = differentially expressed genes, FC = fold change, FDR = false discovery rate, GEO = Gene Expression Omnibus, GO = Gene Ontology, GS = gene significance, GSEA = gene set enrichment analysis, KEGG = Kyoto Encyclopedia of Genes and Genomes, MAD = Median Absolute Deviation, MM = module membership, OSCC = oral squamous cell carcinoma, PLK1 = polo-like kinase 1, PPI = protein–protein interaction, STRING = Search Tool for the Retrieval of Interacting Genes, WGCNA = weighted gene co-expression network analysis.

Keywords: Bioinformatics, CCNA2, CDK1, differentially expressed genes, oral squamous cell carcinoma

1. Introduction

Oral squamous cell carcinoma (OSCC) is a malignant tumor originating from the epithelial tissues of the oral mucosa.[1] OSCC is a relatively common type of oral cancer globally, with a higher incidence among individuals in their middle to late adulthood, particularly those aged 50 and above. Incidence rates vary among regions and populations, but overall trends suggest a higher prevalence in males compared to females.[2,3] OSCC typically exhibits invasive growth patterns, penetrating surrounding tissues, and causing functional impairments that affect basic life functions such as chewing, swallowing, and

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DL and HZ contributed equally to this work.

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The data in this article are from public databases and are exempt from ethical review.

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speech.[4] Diagnosis of OSCC usually requires a tissue biopsy, where microscopic examination of tissue sections is conducted to confirm the tumor type and malignancy. Imaging studies such as X-rays, CT scans, and MRI may also be employed to assess the size and spread of the tumor.[5] Treatment modalities for OSCC include surgical excision, radiation therapy, chemotherapy, or a combination of these, with the choice depending on the tumor's location, size, stage, and the overall health of the patient.[6] The etiology of OSCC is unclear, but major risk factors include prolonged smoking, tobacco chewing, heavy alcohol consumption, chronic oral irritation, and infection with human papillomavirus.[7] Therefore, in-depth molecular research into the mechanisms of OSCC is crucial.

Bioinformatics technology is a field that applies computer science and information technology to biological research, enabling the processing of large-scale, high-throughput biological data to comprehensively understand the complexity of biological systems and reveal molecular-level information.[8,9] In cancer research, bioinformatics technology aids in a deeper understanding of the molecular mechanisms of cancer, individual differences, and more precise diagnosis and treatment.[10] Bioinformatics technology has become a vital tool in contemporary biological and medical research, offering a more in-depth and comprehensive understanding of life's mechanisms and individual variations.[11]

Currently, the relationship between CDK1, CCNA2 genes, and OSCC is not well understood. Therefore, this study aims to use bioinformatics technology to explore the core genes between OSCC and normal tissues, conducting enrichment analysis, and pathway analysis. Public datasets will be utilized to validate the significant roles of CDK1 and CCNA2 genes in OSCC.

2. Methods

2.1. OSCC dataset

In this study, the OSCC datasets GSE74530 and GSE85195 profiles were downloaded from the Gene Expression Omnibus (GEO) database (http://www.ncbi.nlm.nih.gov/geo/), generated from GPL570 and GPL6480. GSE74530 includes 6 OSCC and 6 normal tissue samples, while GSE85195 includes 34 OSCC and 1 normal tissue sample. These datasets were utilized to identify the differentially expressed genes (DEGs) in OSCC.

2.2. Selection of DEGs

The "limma" R package was employed for probe summarization and background correction of the GSE74530 and GSE85195 matrices. The Benjamini-Hochberg method was used to adjust the raw *P* values, and the fold change (FC) was calculated using the false discovery rate (FDR). DEGs were identified with a cut-off of $P < .05$ and FC > 2, and a volcano plot was generated for visualization.

2.3. Weighted gene co-expression network analysis (WGCNA)

First, the Median Absolute Deviation (MAD) of each gene was calculated from the gene expression profiles, and the bottom 50% of genes with the smallest MAD were excluded. The R package WGCNA's goodSamplesGenes method was used to remove outlier genes and samples. WGCNA was then applied to construct a scale-free co-expression network. The adjacency matrix was transformed into a Topological Overlap Matrix, which was then used for gene clustering and module identification based on average linkage hierarchical clustering. Modules were defined with a minimum module size of 30, and modules with a dissimilarity measure <0.25 were merged. The gray module was considered a set of genes that could not be assigned to any module.

2.4. Construction and analysis of protein–protein interaction (PPI) network

The Search Tool for the Retrieval of Interacting Genes (STRING) database (http://string-db.org/) was utilized to collect, score, and integrate protein–protein interaction information. The differential gene list was input into the STRING database to construct a predicted core gene PPI network with a confidence score > 0.4. Cytoscape software was used for biological network analysis and 2D visualization. The PPI network generated by STRING was visualized and core genes were predicted using Cytoscape software. MCODE was applied to identify the most correlated modules, and 2 algorithms (MCC, MNC) were used to calculate the most correlated genes, with the intersection of the results visualized and exported as the core gene list.

2.5. Functional enrichment analysis

Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analyses were conducted to assess gene functions and biological pathways. The clusterProfiler R package was used for enrichment analysis by mapping the selected DEGs to the KEGG API (https://www.kegg.jp/kegg/rest/keggapi.html). Additionally, GO annotations from the org.Hs.e.g..db R package was used as background. Enrichment analysis was performed with a minimum gene set size of 5, a maximum gene set size of 5000, and significance criteria set at a *P* value < .05 and an FDR < 0.25. Furthermore, the Metascape database (http://metascape.org/gp/index.html) was employed for comprehensive annotation and analysis of the identified genes, with visualization and exportation of the results.

2.6. Gene set enrichment analysis (GSEA)

GSEA was carried out using GSEA software (version 3.0) obtained from the Broad Institute website (http://software.broadinstitute.org/gsea/index.jsp). Samples were divided into 2 groups based on OSCC and normal tissue, and the c2.cp.kegg.v7.4.symbols.gmt subset was downloaded from the Molecular Signatures Database. The analysis was conducted with a minimum gene set size of 5, a maximum gene set size of 5000, 1000 permutations, and significance criteria set at a *P* value < .05 and an FDR < 0.25. Additionally, GO and KEGG analyses were performed on the entire genome using GSEA.

2.7. Gene expression heatmap

The heatmap function from the R package was used to visualize the expression levels of core genes identified by the 2 algorithms

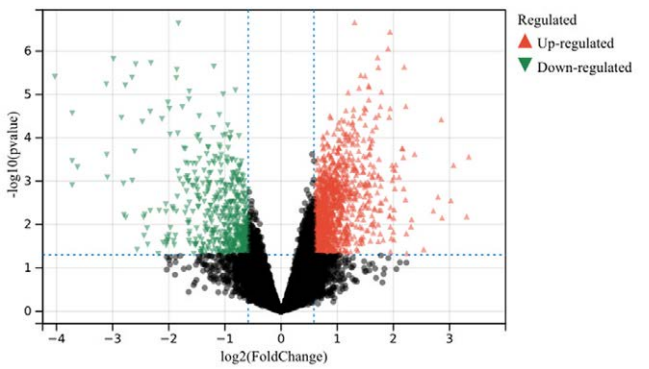

Figure 1. Differential gene analysis. A total of 1756 DEGs. DEGs = differentially expressed genes.

in the PPI network across the GSE74530 and GSE85195 datasets, highlighting the expression differences between OSCC and normal tissue samples.

2.8. Comparative Toxicogenomics Database (CTD) analysis

The CTD database integrates interaction data between chemicals, genes, functional phenotypes, and diseases, providing

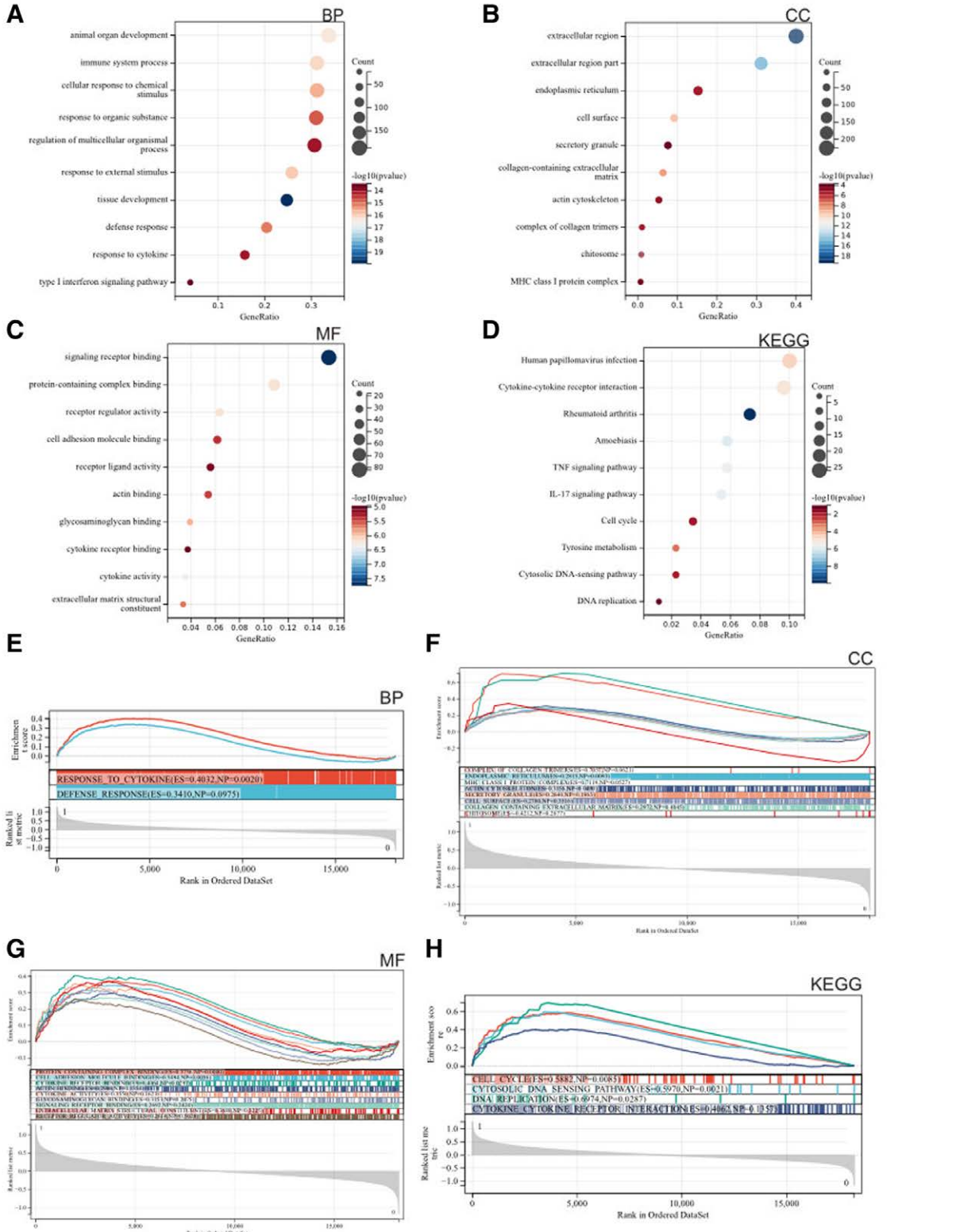

Figure 2. (A–D) GOKEGG enrichment analysis of DEGs. (A) Biological process analysis. (B) Cellular component analysis. (C) Molecular function analysis. (D) KEGG enrichment analysis. (E–H) GSEA of DEGs. (E) Biological process analysis. (F) Cellular component analysis. (G) Molecular function analysis. (H) KEGG enrichment analysis. DEGs = differentially expressed genes, KEGG = Kyoto Encyclopedia of Genes and Genomes.

valuable resources for studying disease-related environmental exposure factors and potential drug mechanisms. Core genes were input into the CTD website to identify the most relevant diseases, and radar charts depicting the expression differences of each gene were created using Excel.

2.9. miRNA–target prediction

TargetScan (www.targetscan.org) was employed as an online database for predicting and analyzing miRNA–target gene interactions. In our study, TargetScan was used to screen for miRNAs regulating the identified central DEGs.

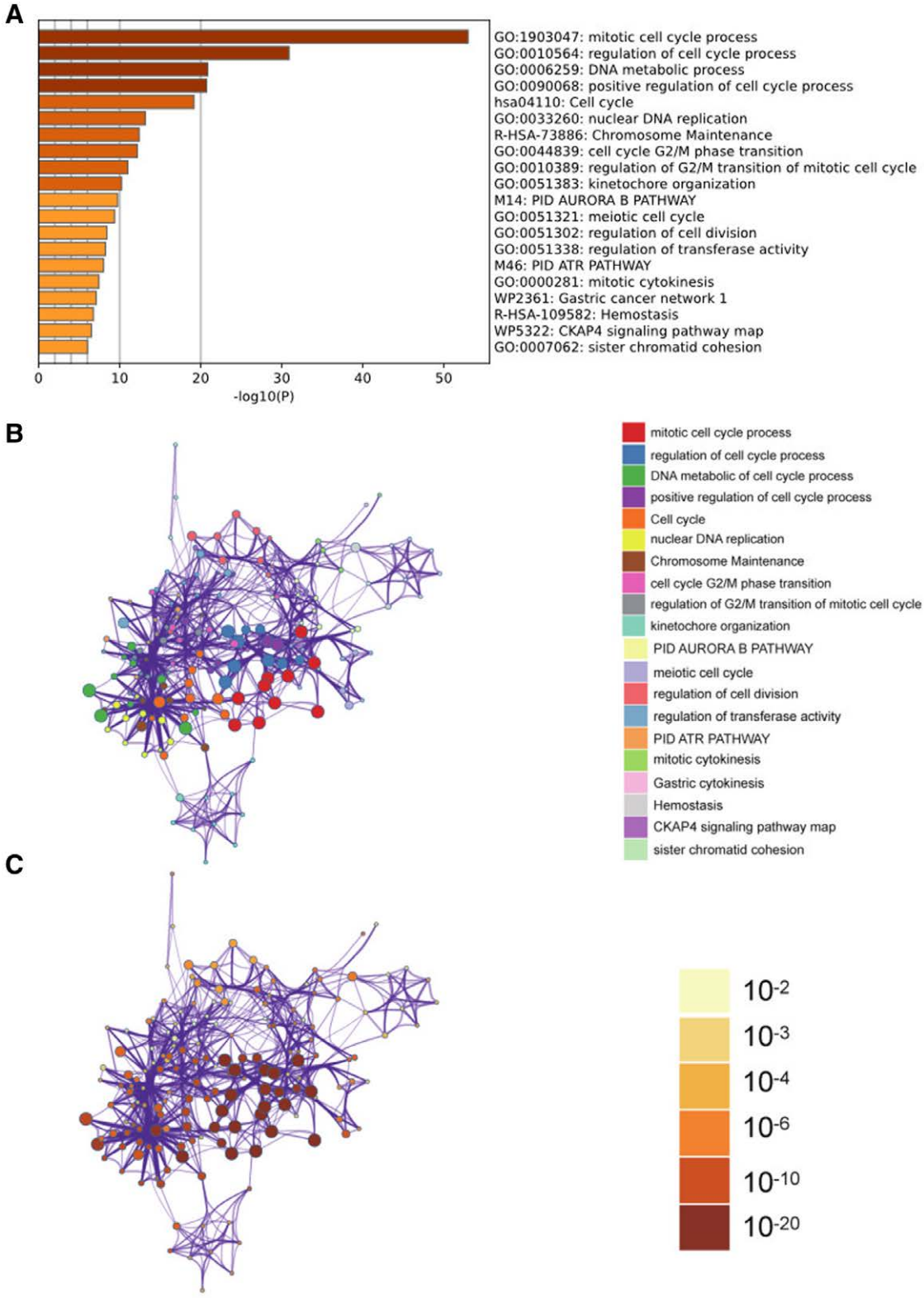

Figure 3. Metascape enrichment analysis. (A) Bar graph of enriched terms across input gene lists, colored by *P* values. (B) Network of enriched terms: colored by cluster ID, where nodes that share the same cluster ID are typically close to each other. (C) colored by *P* value, where terms containing more genes tend to have a more significant *P* value.

3. Results

3.1. Analysis of DEGs

In this study, we identified DEGs from the batch-corrected and merged matrices of GSE74530 and GSE85195, using a predefined cutoff value ($P < .05$). Through R software, a total of 1756 DEGs were identified, and a volcano plot was generated to visualize the results (Fig. 1).

3.2. Functional enrichment analysis

3.2.1. Differentially expressed genes. GO and KEGG analyses were performed on the identified DEGs. Significantly enriched GO and KEGG pathways were selected based on a predetermined significance threshold ($P < .05$). According to GO analysis, the DEGs were mainly enriched in processes such as organic acid catabolic process, condensed chromosome kinetochore, and oxidoreductase activity (Fig. 2A–C). In KEGG analysis, they were primarily concentrated in metabolic pathways, the P53 signaling pathway, and the PPAR signaling pathway (Fig. 2D).

3.2.2. Gene set enrichment analysis. Additionally, GSEA was conducted on the entire genome to identify potential enrichments among non-DEGs and validate the results of DEGs. The results of GO and KEGG enrichment for DEGs showed that they were mainly enriched in organic acid metabolism, P53 signaling pathway, and PPAR signaling pathway (Fig. 2E–H).

3.2.3. Metascape enrichment analysis. Furthermore, we employed METASCAPE for comprehensive annotation and analysis of the DEGs, visualizing the results. The GO enrichment items included the PID PLK1 pathway, mitotic cell cycle, and retinoblastoma gene in tumors (Fig. 3A). Enrichment network visualization with coloring based on significance and P values were performed (Figs. 3B, C and 4), providing a visual representation of the associations and confidence of each enrichment item.

3.3. Weighted gene co-expression network analysis

The selection of the soft-thresholding power is a crucial step in WGCNA. To determine the soft-thresholding power for network topology analysis, a value of 9 was chosen for WGCNA (Fig. 5A). The hierarchical clustering tree of all genes was constructed, important modules were generated, and interactions between these modules were analyzed (Fig. 5B, C). A heatmap of the module-trait correlation (Fig. 5D) and a scatter plot showing the correlation between gene significance (GS)

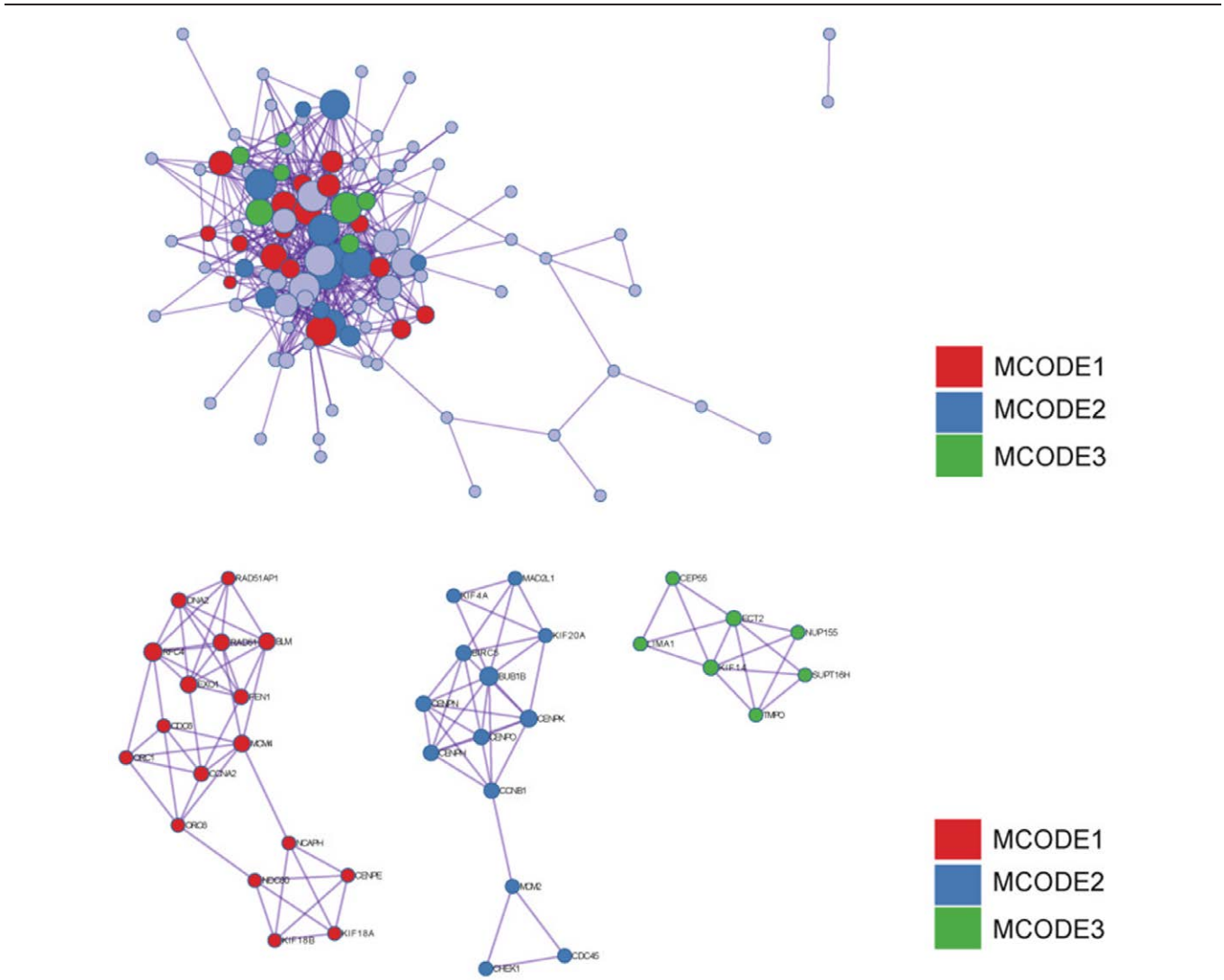

Figure 4. Protein–protein interaction network. MCODE components identified in the gene lists.

and module membership (MM) for hub genes were generated (Fig. 6A).

The module feature vectors' correlation with gene expression was calculated to obtain MM. Based on a cut-off criterion (|MM| > 0.85), 2 highly connected genes were identified as hub genes in clinically significant modules. A Venn diagram was created to visualize the intersection of hub genes selected by WGCNA and DEGs, used for the construction and analysis of the protein–protein interaction network (Fig. 6B).

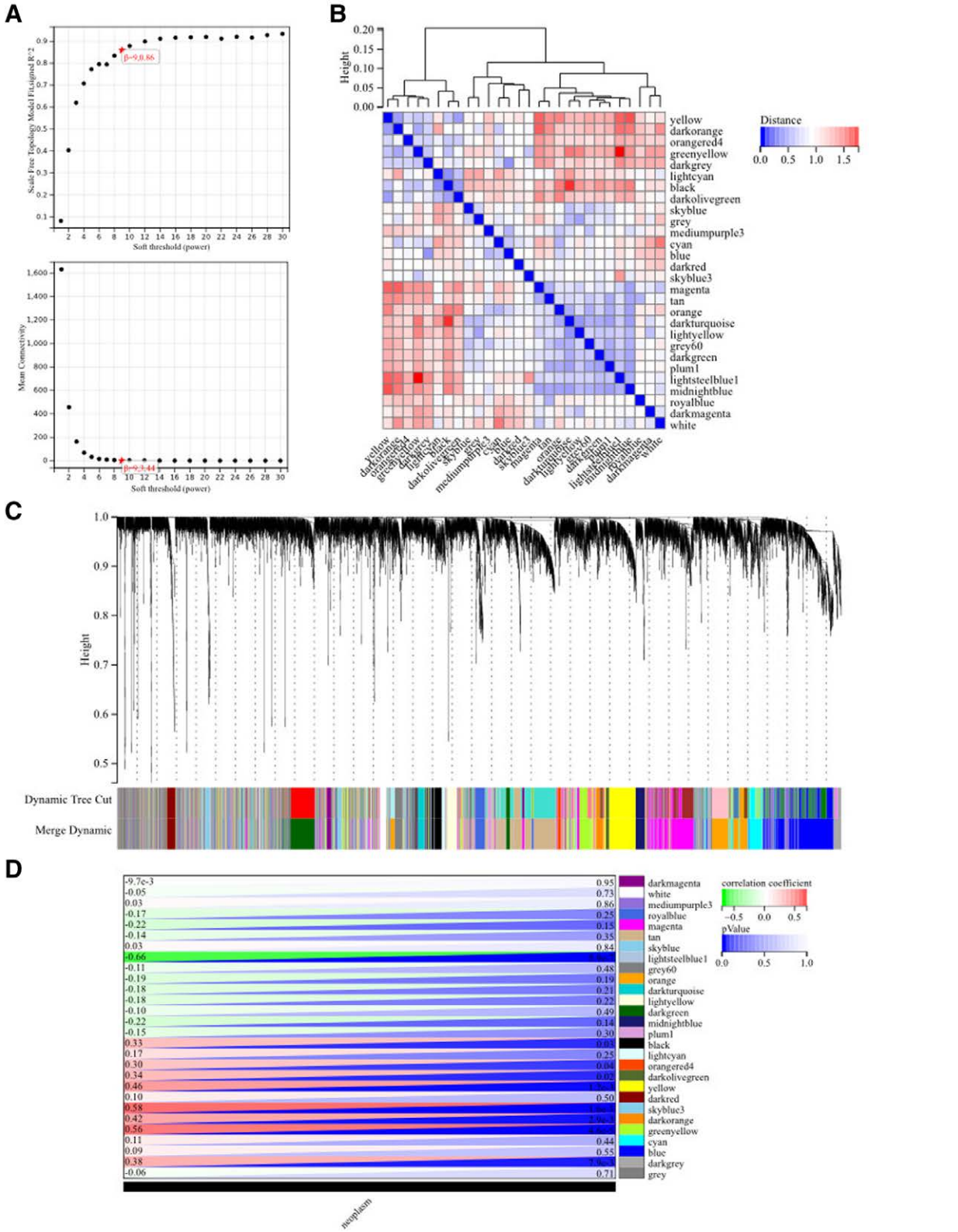

Figure 5. WGCNA. (A) $\beta = 9{,}0.86$. $\beta = 9$, 3.44. (B, C) The hierarchical clustering tree of all genes was constructed, and 28 important modules were generated. (D) The heatmap of correlation between modules and phenotypes. WGCNA = weighted gene co-expression network analysis.

3.4. Construction and analysis of protein–protein interaction (PPI) network

The PPI network of DEGs was constructed using the STRING online database and analyzed with Cytoscape software (Fig. 7A). Core gene clusters were identified (Fig. 7B), central genes were recognized using 2 different algorithms (Fig. 7C, D), and the intersection was visualized with a Venn diagram (Fig. 7E), revealing 6 core genes (BUB1B, CCNB1, KIF20A, CCNA2, CDCA8, CDK1).

3.5. Gene expression heatmap

A heatmap was generated to visualize the expression levels of core genes in samples (Fig. 8A). Core genes (CDK1, CCNA2) were found to be highly expressed in OSCC samples and lowly expressed in normal tissue samples, suggesting a potential regulatory role in OSCC.

3.6. CTD analysis

In this study, the core gene list was input into the CTD website to identify diseases related to core genes, enhancing the understanding of gene-disease associations. Six genes (BUB1B, CCNB1, KIF20A, CCNA2, CDCA8, CDK1) were found to be associated with oral tumors, precancerous lesions, inflammation, immune system diseases, and tongue tumors (Fig. 8B).

3.7. miRNA prediction and functional annotation related to hub genes

In this study, the hub gene list was input into TargetScan to identify related miRNAs, improving the understanding of gene expression regulation (Table 1). It was found that the relevant miRNA for the CDK1 gene is hsa-miR-203a-3p.2, while for the CCNA2 gene, it is hsa-miR-6766-3p, hsa-miR-4782-3p, and hsa-miR-219a-5p.

4. Discussion

OSCC is a common malignant tumor originating from the squamous epithelial tissue of the oral mucosa.[12] The harmful effects of OSCC are primarily manifested in the destruction of oral structures and functions, invasion, and metastasis to the lymphatic system and other organs, leading to a decreased survival rate, especially when metastasis occurs in the cervical lymph nodes.[13,14] In-depth exploration of the molecular mechanisms of OSCC is crucial for targeted drug research. The main findings of this study indicate that the genes CDK1 and CCNA2 are

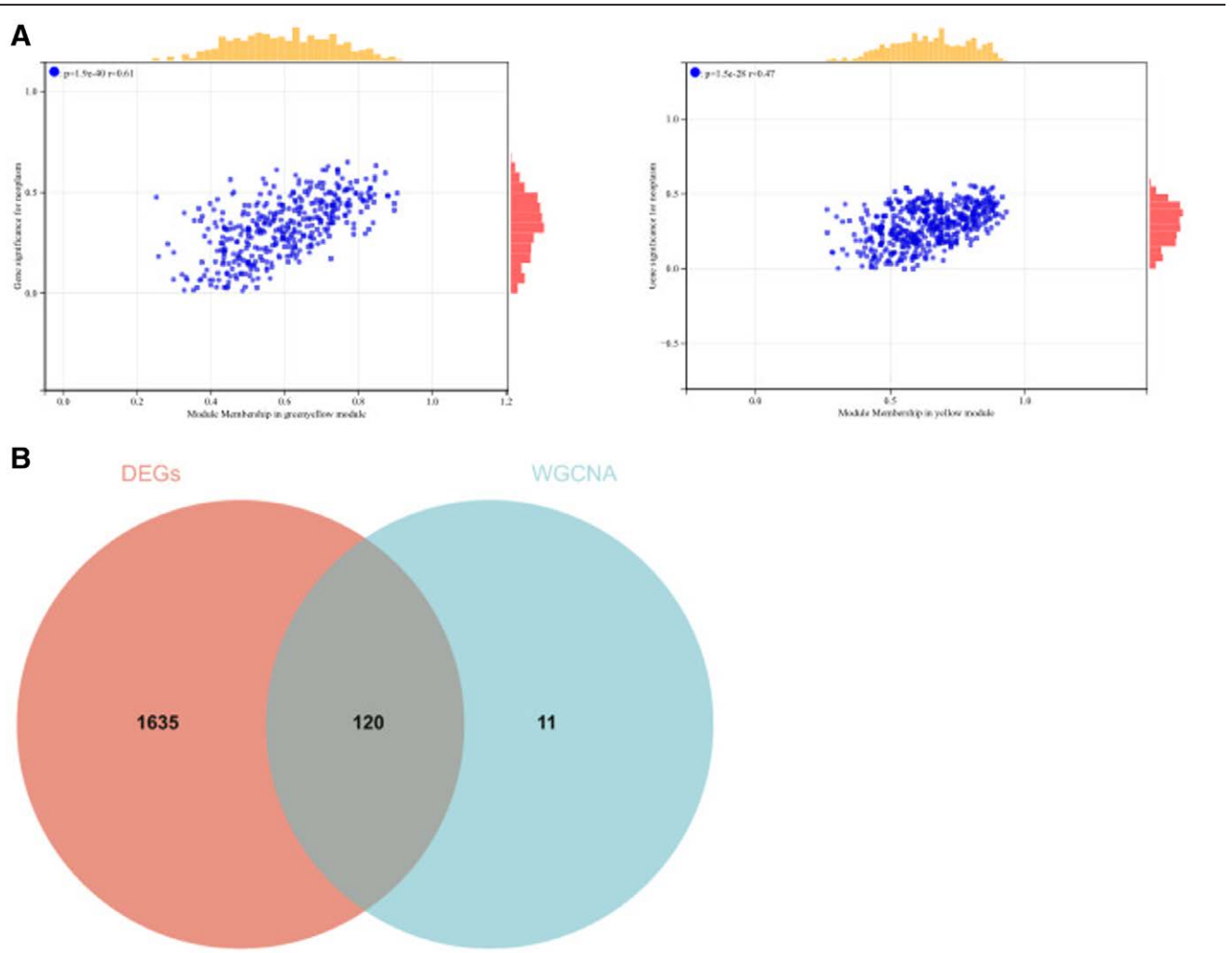

Figure 6. (A) The scatter map of correlation between GS and MM of related hub genes. (B) The DEGs screened by WGCNA and DEGs was used to obtain Venn map. One hundred twenty intersection genes were obtained. DEGs = differentially expressed genes, GS = gene significance, MM = module membership, WGCNA = weighted gene co-expression network analysis.

highly expressed in OSCC, and higher expression of CDK1 and CCNA2 is associated with a poorer prognosis.

Cyclin-dependent kinase 1 (CDK1) is a critical protein kinase belonging to the protein kinase family.[15] CDK1 forms an active complex with its binding partner Cyclin B to create the Mitosis-promoting Factor, regulating the progression of the cell cycle.[16] The cell cycle consists of different stages, including G1 phase, S phase, G2 phase, and M phase. The Mitosis-promoting Factor plays a crucial role in the M phase (mitosis) of the cell cycle, regulating the initiation of mitosis, chromosome replication, nuclear envelope breakdown, and the cell's responsibility for mitosis, facilitating the cell's entry into and completion of the mitotic process. The CDK1/Cyclin B complex regulates various substrates through phosphorylation during the early stages of mitosis, affecting multiple cell cycle-related proteins, including structural proteins, chromosome-related proteins, and cell cycle regulatory proteins, driving the cell's entry and progression through mitosis. These substrates include structural proteins and other cell cycle regulatory proteins.

CDK1 is a key protein kinase in cell cycle regulation, interacting with cell cycle proteins such as Cyclin E and Cyclin A, and is essential for the normal progression of the cell cycle and the mitotic process. CDK1 participates in checkpoint control of the cell cycle, ensuring smooth transitions between different stages of the cell cycle, including the activation and inactivation of checkpoints, as well as cell cycle arrest when the cell

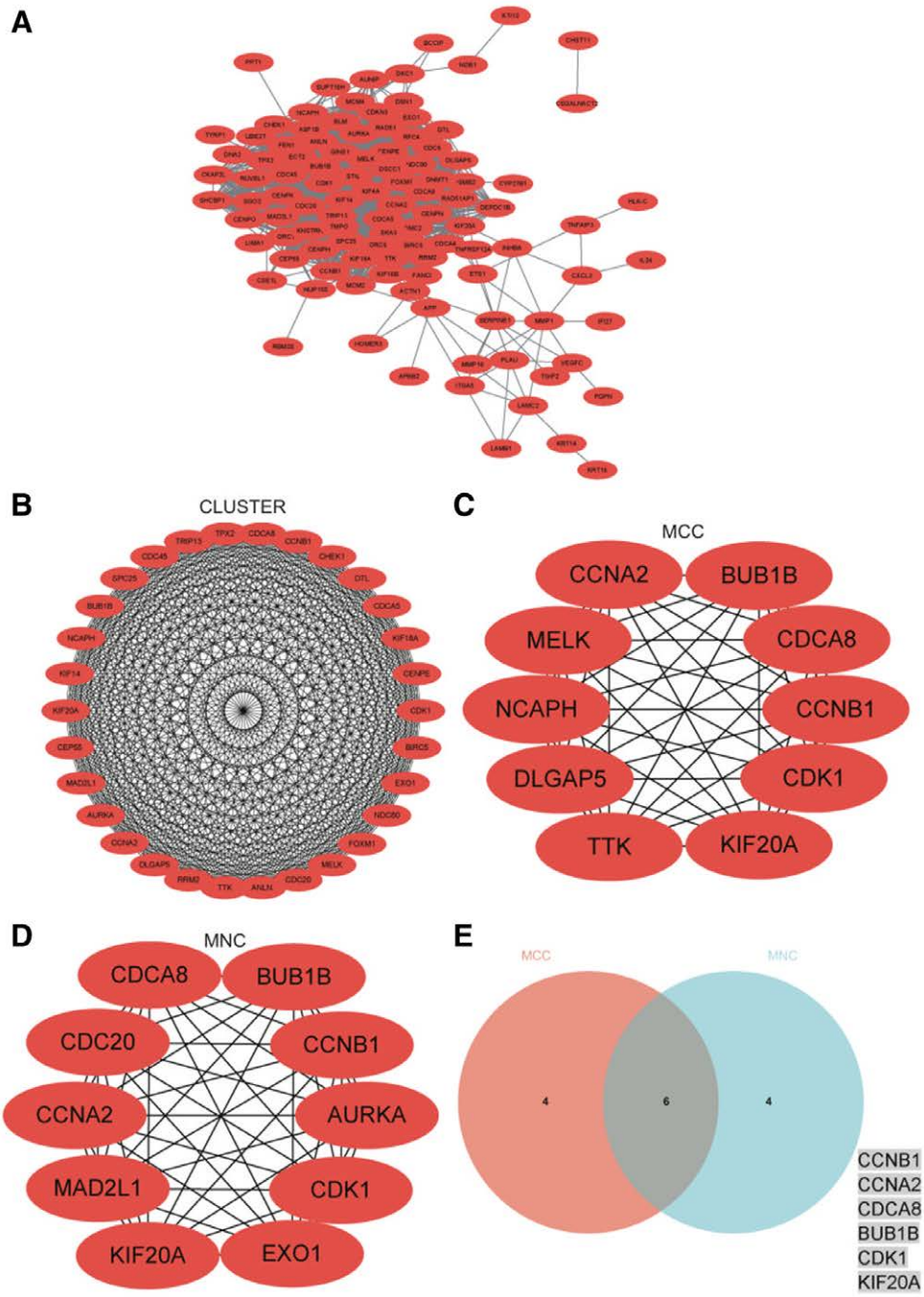

Figure 7. Construction and analysis of protein–protein interaction (PPI) networks. (A) PPI network of DEGs. (B) CLUSTER was used to identify the central gene. (C) MCC was used to identify the central gene. (D) MNC was used to identify the central gene. (E) Six core genes (BUB1B, CCNB1, KIF20A, CCNA2, CDCA8, CDK1) were obtained by merging using Venn diagrams. DEGs = differentially expressed genes.

undergoes DNA damage.[17] CDK1 regulates different stages of the cell cycle by phosphorylating cell division-related proteins, chromosome-related proteins, and other cell cycle-related proteins. Downregulation of CDK1 is associated with the differentiation of human neurons, muscle cells, retinal progenitor cells, and leukemia cells. Inhibition of CDK1 can trigger differentiation in hematopoietic, hair, and neuronal cells.[18]

CDK1 is downstream of the mitotic signaling transcription and directly reflects the proliferative capacity of cells. The cell cycle control mediated by CDK1 may be related to precise reproduction and cell size homeostasis.[19] High expression of CDK1 may be associated with aggressive growth of tumors, lymph node metastasis, and poor prognosis. Inhibition of CDK1 can block the cell cycle and suppress abnormal proliferation of cancer cells.[20] Previous studies have indicated that the long non-coding RNA CASC2 inhibits the growth, migration, and invasion of OSCC by downregulating CDK1.[21] CDK1 is a catalytic subunit of a protein kinase complex that induces cells to enter mitosis, and NPM, CDK1, and NDRG1 are highly expressed in OSCC.[22] The expression of CDK1 in OSCC has clinical significance, and its overexpression is related to the malignancy and prognosis of OSCC.[23] The expression of CDK1 in OSCC tissues is significantly increased compared to normal oral tissues. This overexpression may be related to abnormal regulation of the cell cycle and uncontrolled proliferation of tumor cells. CDK1 plays a role in promoting mitosis

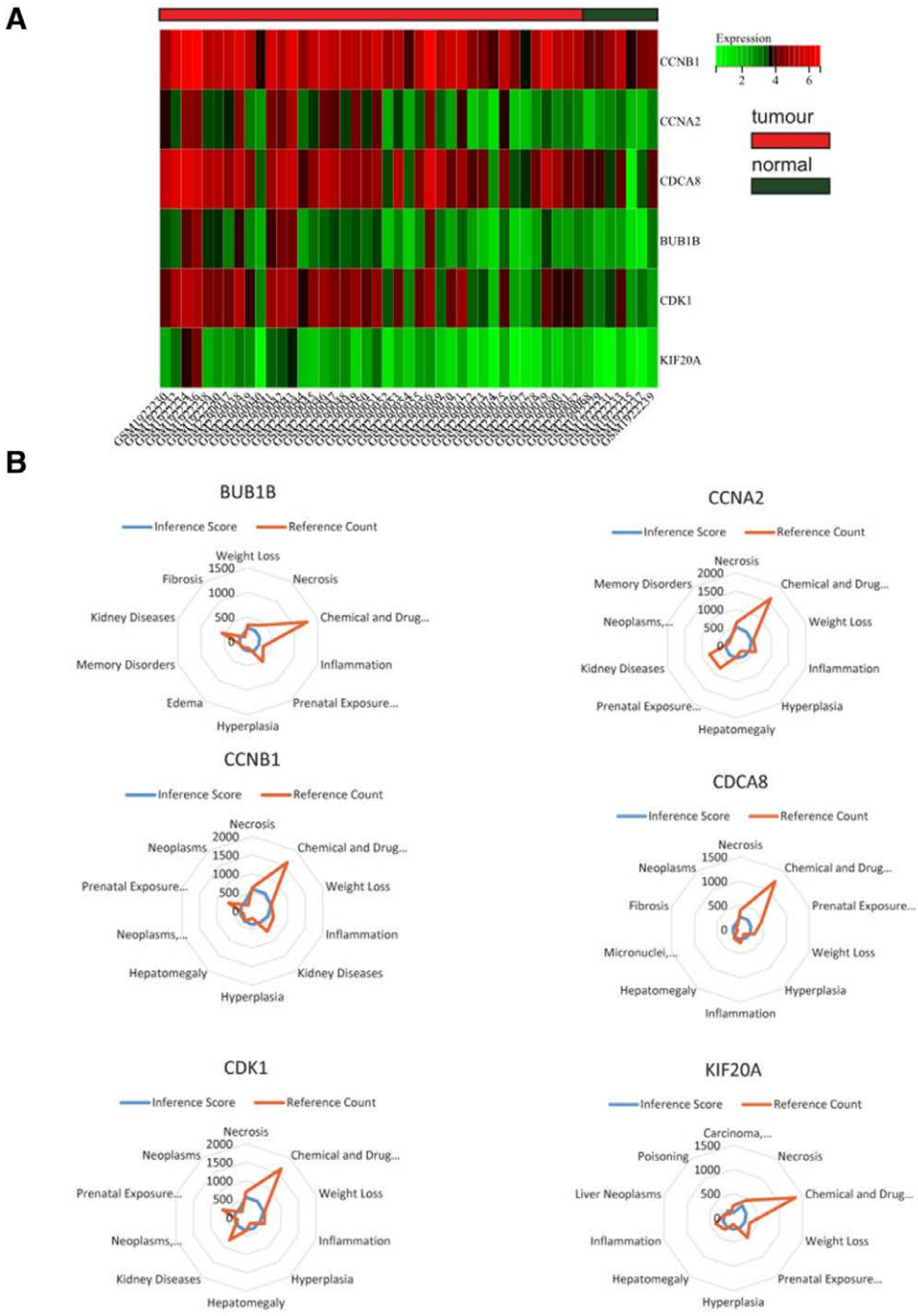

Figure 8. (A) The heatmap depicting the expression levels of differentially expressed genes related to ferroptosis in the merged matrix of GSE74530 and GSE85195 datasets. (B) CTD analysis. Six genes (BUB1B, CCNB1, KIF20A, CCNA2, CDCA8, CDK1) are associated with liver tumors, hepatocellular carcinoma, invasive tumors, and end-stage liver disease. CTD = Comparative Toxicogenomics Database.

Table 1

A summary of miRNAs that regulate hub genes.

Number	Gene	MIRNA		
1	CCNB1	hsa-miR-183-5p.1		
2	CCNA2	hsa-miR-6766-3p	hsa-miR-4782-3p	hsa-miR-219a-5p
3	CDCA8	hsa-miR-133b	hsa-miR-133a-3p.2	
4	BUB1B	none		
5	CDK1	hsa-miR-203a-3p.2		
6	KIF20A	hsa-miR-153-3p		

during the M phase of the cell cycle, and its overactivation may promote uncontrolled proliferation of tumor cells, contributing to the development of OSCC.

Cell cyclin A2 (CCNA2) is located on chromosome 4q27 in humans, with a total length of 7489 bp, and is expressed in almost all tissues of the human body.[24] CCNA2 is a protein-coding gene that encodes a protein belonging to the highly conserved cyclin family, members of which have the function of regulating the cell cycle. It can activate Cyclin-Dependent Kinase 2, thereby promoting transitions through the G1/S and G2/M phases.[25] Diseases associated with CCNA2 include retinoblastoma and adenocarcinoma, and its related pathways include proteasome-mediated degradation regulated by activated PAK-2p34 and homologous repair. GO annotations associated with this gene include protein kinase binding. An important homologous gene of this gene is CCNA1.[26]

CCNA2 is a cell cycle protein present in mammals, promoting progression through the S phase and G2-M phase transition by binding to CDK during mitosis.[27] As an immunobiological marker covering the tumor microenvironment and treatment response in various cancer types, CCNA2 is closely associated with the occurrence and development of multiple tumors, potentially participating in tumorigenesis and progression through its influence on Epithelial-Mesenchymal Transition and metastasis.[28,29] Drug genomic analysis reveals CCNA2 as a predictive biomarker for sensitivity to polo-like kinase 1 (PLK1) inhibitors in gastric cancer, where elevated expression of CCNA2 in gastric cancer cell lines and primary tumors leads to increased sensitivity to PLK1 inhibitors.[30] Comprehensive analysis identifies CCNA2 as a potential biomarker for immunotherapy in breast cancer.[31] Furthermore, research suggests that E2F1 promotes the oncogenicity of triple-negative breast cancer by transcriptionally regulating the expression of CCNA2, making E2F1 and CCNA2 potential targets for effective treatment of triple-negative breast cancer.[32]

In cancer research, overexpression or abnormal activation of Cyclin A2 may be associated with the occurrence and development of tumors. CCNA2 can promote cancer proliferation and invasion through immune deficiency and natural killer cell-mediated cytotoxic pathways. Aberrant expression of Cyclin A2 may disrupt the normal cycling of cells, thus facilitating tumor formation.[33,34] OSCC is often associated with abnormalities in cell cycle regulation, and Cyclin A2 plays a crucial role in cell cycle regulation. PKMYT1 regulates the proliferation and Epithelial-Mesenchymal Transition of OSCC cells by targeting CCNA2.[35] Therefore, it is speculated that the CCNA2 gene may play a significant role in the progression of OSCC.

Despite rigorous bioinformatics analysis in this study, there are still limitations. The research did not conduct animal experiments involving gene overexpression or knockout to further validate its functionality. Therefore, future research should delve into this aspect for a more comprehensive understanding.

5. Future research directions and prospects

In the research of OSCC, further investigation can be directed toward targeting the key players, CDK1 and CCNA2, considering their crucial roles in disease progression. The development of drugs targeting CDK1 and CCNA2 involves chemical synthesis, drug screening, and computational biology approaches, exploring effective inhibitors which could be small molecules, antibody drugs, or other targeted therapy methods. Preclinical studies involve evaluating the efficacy and safety of these new drugs in cell lines, animal models, or ex vivo tissues, providing essential preliminary information for clinical trials. Clinical trial design includes designing trials targeting CDK1 and CCNA2 inhibitors to assess their efficacy and safety in treating OSCC patients, possibly involving monotherapy, combination therapy, or novel adjuvant treatment strategies. Discovery of molecular biomarkers involves exploring the potential of CDK1 and CCNA2 as prognostic markers for OSCC, validating their associations with disease progression, treatment response, and patient prognosis through large-scale clinical studies. Collaboration with clinicians and the pharmaceutical industry ensures the smooth translation of research findings into clinical practice, involving the formulation of treatment guidelines, training healthcare professionals, and promoting drug development. Incorporating the detection of CDK1 and CCNA2 into the diagnosis and treatment of OSCC enables personalized therapy, selecting the most appropriate treatment approach based on the molecular characteristics of the patient's tumor. Leveraging expertise from multiple disciplines including bioinformatics, molecular biology, pharmacology, and clinical medicine drives research and development in OSCC treatment. Translating CDK1 and CCNA2 as novel targets for OSCC into clinical practice offers more effective treatment options for patients.

6. Conclusion

CDK1 and CCNA2 play crucial roles in OSCC. Elevated expression of CDK1 and CCNA2 genes in OSCC is associated with a poorer prognosis, providing a new direction for the diagnosis and treatment of OSCC.

Author contributions

Conceptualization: Junbo Zhang, Yongbin Di.
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Visualization: Junbo Zhang.
Writing—review & editing: Junbo Zhang, Yongbin Di.
Supervision: Yongbin Di.
Data curation: Bohao Zhang, Tianke Li, Dan Li, Haolei Zhang.
Formal analysis: Bohao Zhang, Tianke Li, Dan Li, Haolei Zhang.
Software: Tianke Li.
Writing—original draft: Tianke Li, Dan Li, Haolei Zhang.

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