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ORIGINAL RESEARCH

Lidocaine as a Potential Therapeutic Agent in Colorectal Cancer: A Study of Gene Expression and Prognosis

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Background: Colorectal cancer (CRC) is a significant contributor to cancer-related mortality globally. Despite the availability of treatments such as surgery, chemotherapy, and radiotherapy, these interventions are often accompanied by severe side effects and suboptimal patient outcomes. Recent studies have suggested that lidocaine, a widely used local anesthetic, may possess anti-tumor properties in various cancer types. This study aims to explore the impact of lidocaine on CRC cell lines, HCT 116 and SW480, to evaluate its potential as a therapeutic agent.

Methods: In vitro assays were conducted to assess the effect of lidocaine on the proliferation, migration, and invasion of CRC cells. The suppression of cell proliferation and induction of apoptosis were confirmed using colony formation, EdU, and TUNEL assays. RNA sequencing was performed on lidocaine-treated HCT 116 cells to identify differentially expressed genes and enriched biological pathways. A prognostic signature based on 16 genes was developed and validated using clinical data.

Results: Lidocaine significantly inhibited the proliferation, migration, and invasion of CRC cells in a dose-dependent manner. The assays confirmed that lidocaine suppressed cell proliferation and induced apoptosis. RNA sequencing revealed 8002 differentially expressed genes in lidocaine-treated HCT 116 cells, with significant enrichment of key pathways such as the estrogen signaling pathway and MAPK pathway. A prognostic signature based on 16 genes was developed and validated, providing a predictive model for patient survival. These findings suggest that lidocaine has potential as a therapeutic agent for CRC treatment, although further in vivo studies are required to clarify its mechanisms and optimize its clinical application.

Keywords: lidocaine, colorectal cancer, lasso-cox prognosis analysis, prognostic model, immunity

Introduction

Colorectal cancer (CRC) has become the fourth most deadly cancer globally.[1] In addition to the male sex and increasing age, both hereditary and environmental risk factors play a significant role in CRC development.[2] Tumor metastasis is the primary cause of mortality in 90% of CRC cases, with a 5-year survival rate of less than 20%. Traditional CRC treatments, including surgery, chemotherapy, and radiotherapy, have limited effectiveness and are associated with significant side effects, resulting in suboptimal patient outcomes. Recent advancements in targeted therapy, immunotherapy, and other therapeutic approaches have improved CRC treatment.[3,4] However, adverse reactions often occur during treatment, severely impacting the patient's quality of life.[5] Therefore, there is an urgent need to explore novel and effective treatment strategies to improve survival outcomes.

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Lidocaine is one of the most commonly used local anesthetics for surgical procedures.[6] It is utilized in clinical scenarios for local anesthesia of the skin and mucosa, as well as regional nerve blockage, and it possesses anti-inflammatory and antibacterial effects.[7–9] Recently, it has been found that lidocaine exerts anti-tumor effects in various types of cancer.[10–13] Lidocaine has demonstrated protective effects against breast cancer cells and the ability to inhibit the proliferation and metastasis of epithelial ovarian cancer (EOC) through the Wnt/β-catenin pathway, thereby regulating EOC progression.[14] Lidocaine may also influence the malignancy of colon cancer cells by modulating the circ_ANO5/miR-21-5p/LIFR axis.[15]

Additionally, it has been reported that lidocaine can induce apoptosis and inhibit proliferation in CRC cells,[16,17] though the mechanism remains unclear.

This study hypothesizes that lidocaine inhibits the malignant phenotypes of colorectal cancer (CRC) cells by regulating the MAPK signaling pathways. Bioinformatics was used to elucidate the intricate relationship between lidocaine and colorectal cancer (CRC). A prognostic signature was constructed to predict survival outcomes. A deeper understanding of lidocaine's regulatory role in oncogenesis could open new avenues for cancer treatment.

Materials and Methods

Cell Culture

Colon cancer cell lines SW480 and HCT116 were sourced from Zhong Qiao Xin Zhou Biotechnology (Shanghai, China). All cells were cultured in RPMI1640 medium (Gibco, USA). The culture medium was supplemented with 10% fetal bovine serum (Wisent, China), 100 mg/mL streptomycin, and 100 U/mL penicillin. Cells were incubated in a humidified atmosphere with 5% CO_2 at 37 °C. Cells in the control group were treated with normal saline of the same volume as those in the experimental group, and other culture conditions were the same.

CCK-8 Assay

To ascertain the optimal seeding density of colon cancer cells within a 96-well plate, we meticulously dispensed 2000 cells into each well, ensuring triplicate to sextuplicate wells per group for reliability. Subsequently, we introduced a precise volume of CCK-8 solution, corresponding to one-tenth of the culture medium, into each well. Additionally, we established blank control wells, containing an equivalent volume of cell culture medium and CCK-8 solution but devoid of cells, to account for any background absorbance. Following a two-hour incubation in the cell culture incubator, we employed a microplate reader to quantify the absorbance at 450 nm. Furthermore, we consistently measured the absorbance at 24 hours post-incubation, using the same microplate reader, to track cellular proliferation dynamics. The experimental doses (366.4 μM and 250.9 μM) were determined based on pre-experimental results and close to tissue concentrations after local anesthesia (50–100 μM), but further validation of their clinical translational potential is needed.

Colony Formation Assay

The colon cancer cells in the exponential growth phase were selected and subjected to conventional digestion and passage methods to prepare a cell suspension. After cell counting, 500 cells were added to each well of a six-well plate. The culture dish was gently shaken in a crisscross direction to ensure even cell dispersion. The culture dish was then placed in a 37°C incubator with 5% CO_2 for 2–3 weeks. During this period, fresh culture medium was replaced as needed based on changes in the pH of the culture medium. When macroscopic clones appeared in the culture dish, the culture was terminated, and the culture medium was discarded. The cells were carefully rinsed twice with PBS and allowed to air-dry. They were then fixed with methanol for 15 minutes, and after discarding the methanol, they were allowed to air-dry again. The cells were stained with 0.1% crystal violet stain for 10 minutes, and the stain was gently washed away with running water. After air-drying, the cells were photographed using a digital camera.

Transwell Migration and Invasion Assay

Add 50μL of serum-free medium to each well of the Transwell chamber and hydrate the basement membrane at 37°C for 30 minutes at room temperature. Place the chamber in a 24-well plate, and take colon cancer cells in the exponential

growth phase. Using routine digestion and passaging methods, prepare a cell suspension. After counting the cells, add 2000 cells and 500μL of serum-free medium to the upper chamber of the Transwell chamber. Add 600 μL of medium containing 10% FBS to the lower chamber of the 24-well plate. Gently shake the culture dish in a cross-shaped direction to evenly disperse the cells. Incubate the dish at 37°C, 5% CO_2 for 24 hours. Remove the Transwell chamber, discard the culture medium in the well, wash twice with calcium-free PBS, fix with methanol for 30 minutes, and air-dry the chamber appropriately. Stain with 0.1% crystal violet for 20 minutes, gently wipe off the unmigrated cells on the upper layer with a cotton swab, and wash three times with PBS. Observe the cells under a fluorescence microscope in five random fields, count, take the average, and perform statistical analysis.

EdU Staining

To investigate cell proliferation, a specific protocol was followed for cell culture and EdU incorporation. Initially, an appropriate amount of cells were seeded into a 6-well plate and allowed to recover overnight before applying the desired treatment. Next, a 2X EdU working solution was prepared, ensuring a final EdU concentration of 10 μM, which could be adjusted based on the cell type and experimental conditions. Subsequently, the pre-warmed 2X EdU working solution was added to the wells, ensuring the correct final EdU concentration while accounting for the volume of the culture medium. The cells were then incubated for 2 hours, with the incubation time potentially adjusted based on the cell type. Afterward, the culture medium was removed, and the cells were fixed with a fixative solution followed by washing with a wash buffer. The cells were then permeabilized with a permeabilization solution, washed again, and prepared for subsequent steps. For each well, 0.5 mL of Click reaction cocktail was added, and the cells were incubated at room temperature for 30 minutes in the dark. The Click reaction cocktail was then aspirated, and the cells were washed three times with the wash buffer for 3–5 minutes each. Following nuclear staining, the cells were ready for observation under a fluorescence microscope.

Tunel Staining

After processing, the colon cancer cells were washed once with PBS and fixed with 4% paraformaldehyde for 30 minutes. They were then washed once with PBS or HBSS. Subsequently, the cells were incubated with PBS containing 0.3% Triton X-100 for 5 minutes at room temperature. Following this, they were washed twice with PBS or HBSS. Next, 50μL of TUNEL detection solution was added to the samples, which were then incubated in the dark at 37°C for 60 minutes. Afterward, the samples were washed three times with PBS or HBSS. Finally, the samples were mounted with anti-fluorescence quenching mounting medium and observed under a fluorescence microscope.

Transcriptomic Profiling by RNA-Seq

For bulk RNA-seq analysis, total RNA was extracted using the QIAzol method and purified with the Qiagen RNeasy kit. Libraries were prepared using the Illumina TruSeq RNA Library Prep Kit v2 and sequenced on the Illumina HiSeq 2000 platform with a single-end read length of 76 nucleotides. The raw RNA-seq reads were aligned to the GRCm38/mm10 reference genome using the STAR aligner. HTSeq-count was used to quantify raw reads for each gene in each sample. Differential expression analysis was performed with edgeR, and pathway enrichment analysis was conducted using GSEA software. Differential expression analysis was performed by edgeR and a total of 8002 differentially expressed genes were identified. Subsequent pathway enrichment analysis by GSEA showed a significant correlation between MAPK and estrogen signaling pathways.

Data Collection

Utilizing meticulous curation from reputable databases including GeneCards, Online Mendelian Inheritance in Man (OMIM), Pharmacogenetics and Pharmacogenomics Knowledge Base (PharmGKB), DisGeNET for gene-disease associations, and Therapeutic Target Database (TTD), we have meticulously identified and acquired disease-relevant genes tightly associated with colorectal cancer (CRC). To ensure the comprehensiveness and accuracy of our data, we employed a dual-track data collection strategy: the training gene set was sourced from the authoritative The Cancer Genome Atlas (TCGA), while the validation gene set was meticulously selected from the Gene Expression Omnibus

(GEO) database. Furthermore, to visually illustrate the differential expression of these genes between adjacent non-tumorous tissues and tumorous tissues, we incorporated immunohistochemistry images from the Human Protein Atlas (HPA), providing invaluable visual evidence of gene expression. The prognostic gene set was obtained by integrating TCGA clinical data with published literature on prognostic markers for CRC.

Core Gene Analysis

This study conducted an in-depth analysis of RNA-seq data from TCGA, comparing tumor and adjacent normal tissues to reveal subtle gene expression changes. Using heatmaps and boxplots, we visualized core gene expression patterns. Gene correlation analysis uncovered potential regulatory networks. After rigorous filtering, we identified differentially expressed genes (DEGs) with significant clinical implications.

Construction of Lasso Composite Regression Prediction Model

To enhance predictive accuracy and interpretability, we developed a Lasso Composite Regression Prediction Model. This model integrates Lasso regression's strength in variable selection and regularization, mitigating multicollinearity and overfitting. By crafting a composite model with carefully selected and optimized variables, we achieved robust forecasts. We explored the dataset, identified relevant variables, and employed Lasso regression to select significant and non-redundant predictors. The selected variables were then fitted into a regression framework, calibrated to minimize prediction error. Cross-validation ensured model robustness. Our focus on interpretability yielded a model that is both accurate and easy to understand, translating insights into actionable strategies. Additionally, we used Cox regression analysis to determine the prognostic value of genes, identifying CRC prognostic genes through Lasso-Cox method and evaluating their performance with Kaplan-Meier curves.

Validation of the Lasso-Cox Regression Prediction Model

The proposed Lasso-Cox regression model was validated using CRC transcriptome and clinical data from GEO datasets. ROC analysis with pROC package in R assessed model accuracy. Risk curves, scatter plots, and heatmaps illuminated the relationship between risk and survival. Univariate Cox regression analysis constructed forest plots, revealing individual variable contributions. A nomogram was developed using the "rms" package, facilitating prognostic assessment and survival prediction. The integrated techniques ensured a thorough validation of the model.

Correlation Between Prognostic Models and Tumor Immunity

To investigate the intricate interplay between prognostic models and tumor immunology in CRC, we leveraged the TIMER2.0 database for immune cell abundance data. We analyzed immune cell levels using bar graphs and correlation plots. Further, we utilized SangerBox to explore the targeted relationships between three prognostic genes' expression and immune cell subsets/checkpoints. Additionally, IOBR R package and TCGA data facilitated the generation of Kaplan-Meier survival curves, revealing the associations between stromal/immune cell abundance and survival rates. This comprehensive approach deepened our understanding of prognostic implications and suggested potential therapeutic strategies leveraging the immune system in CRC.

Statistics

Statistical analysis utilized GraphPad Prism v8.0. Student's *t*-test was used for group comparisons. Data are presented as mean ± SD. A p-value less than 0.05 was deemed statistically significant.

Results

Lidocaine Suppresses the Cell Proliferation, Migration and Invasion of Colorectal Cancer

To explore the effect of lidocaine (Figure 1A) on colorectal cancer development, HCT 116 and SW480 cells were treated with different doses of lidocaine for 24 hours. Cell viability was assessed after 24 hours using CCK8 assays. Lidocaine

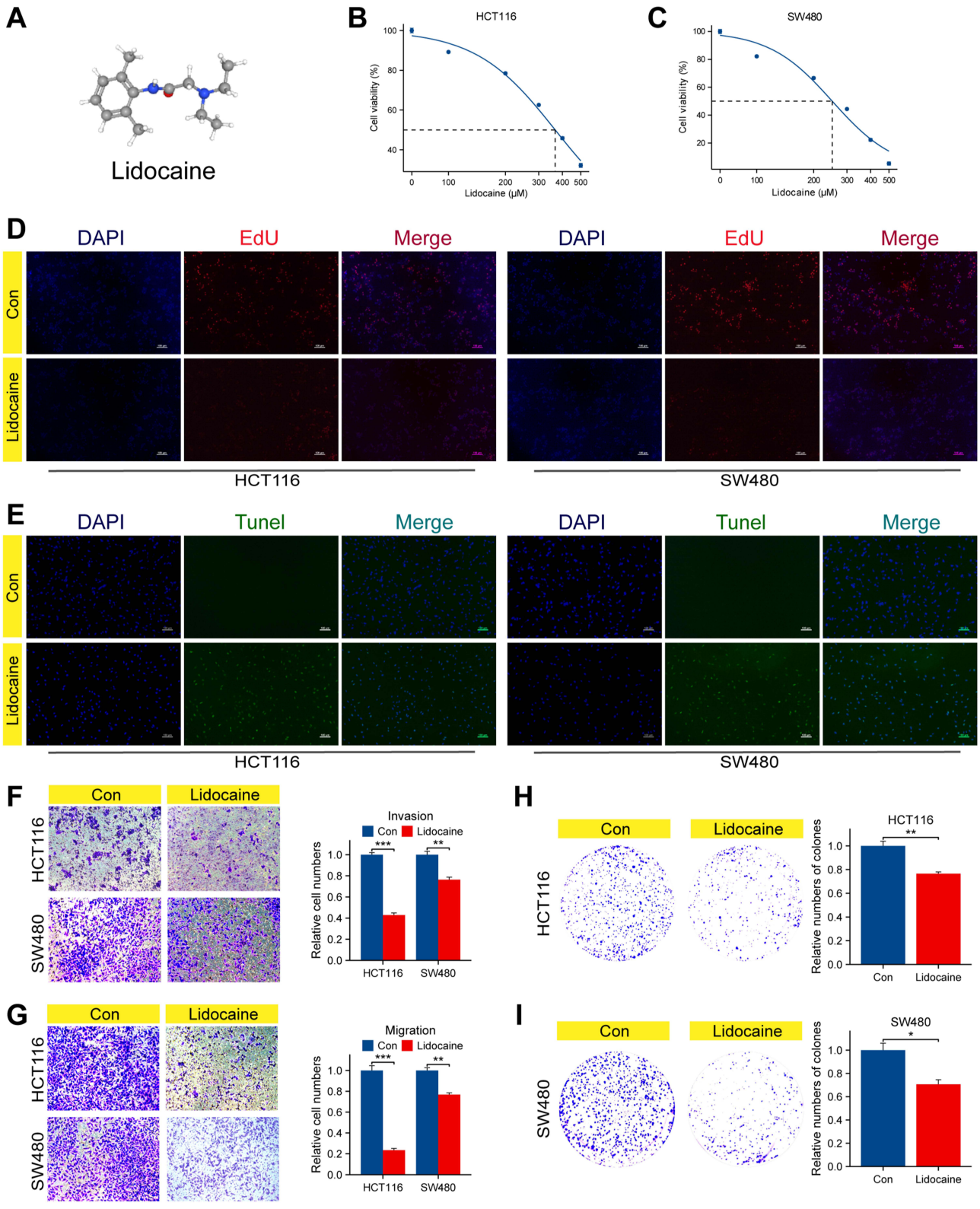

Figure 1 Lidocaine suppresses the cell proliferation, migration and invasion of colorectal cancer. (**A**) The chemical structure of Lidocaine. (**B** and **C**) HCT 116 cell line and SW480 cell line were treated with different concentrations of Lidocaine (n=3). (**D**) EdU assay was used to assess the growth of HCT 116 cell line and SW480 cell line after Lidocaine treatmen (n=3)t. (**E**) Tunel assay was used to assess the apoptosis of HCT 116 cell line and SW480 cell line after Lidocaine treatment (n=3). (**F** and **G**) Cell Invasion and migration assay were used to evaluate the influence of Lidocaine on HCT116 and SW480 cell line (n=3) (x 200). (**H** and **I**) Colony formation assay was used the evaluate the influence of Lidocaine on HCT116 and SW480 cell line (n=3). *p < 0.05;**p < 0.01; ***p < 0.001.

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significantly inhibited cell proliferation in both HCT 116 and SW480 cells in a concentration-dependent manner. Based on these results, we selected a lidocaine dose of 366.4 μM for HCT 116 cells (Figure 1B) and 250.9 μM for SW480 cells (Figure 1C) for subsequent experiments. Colony formation and EdU assays further demonstrated that lidocaine suppressed the proliferation of HCT 116 and SW480 cells (Figure 1D, H and I). Tunel assay results showed that lidocaine induced apoptosis in HCT 116 and SW480 cells (Figure 1E). Transwell assays indicated that lidocaine was sufficient to inhibit the migration and invasion of HCT 116 and SW480 cells (Figure 1F and G). In summary, lidocaine suppresses the proliferation, migration, and invasion of colorectal cancer cells.

RNA Sequencing Analysis Reveals Transcriptional Regulation of Lidocaine in Colorectal Cancer Cells

RNA sequencing was conducted on HCT 116 cells treated with lidocaine. A total of 8002 differentially expressed genes were identified in lidocaine-treated HCT 116 cells compared to untreated cells, including 884 upregulated and 451 downregulated genes (Figure 2A). To elucidate the potential functions of these differentially expressed genes, we performed GO and KEGG enrichment analyses (Table S1, 2). GO enrichment results indicated that lidocaine was involved in functions such as "intermediate filament organization", "intermediate filament cytoskeleton organization", "intermediate filament-based process", "organophosphate catabolic process", "intermediate filament", "intermediate filament cytoskeleton", "collagen trimer", "endoplasmic reticulum lumen", "lysophospholipase activity", "extracellular matrix structural constituent", "3',5'-cyclic-AMP phosphodiesterase activity", and "phosphoric ester hydrolase activity" (Figure 2B). KEGG enrichment results showed that these genes are involved in the "Estrogen signaling pathway", "MAPK signaling pathway", "Staphylococcus aureus infection", "Morphine addiction", among others (Figure 2C).

A Venn diagram showed that 30 overlapping genes are shared between lidocaine target genes and CRC-related genes associated with overall survival (OS) (Figure 2D). These 30 genes were further analyzed using the lasso-Cox method via the R package glmnet to resolve the overlap issue (lambda.min = 0.0159) (Figure 2E and F). The risk score distribution and survival status are shown in Figure 2G, indicating that as the risk score increases, the patient mortality rate rises (Riskscore=(0.076)*PANX2+(0.0231)*AVPR2+(0.0948)*ULBP2+(0.1398)*CLEC18B+(0.5042)*NTN5+(0.1012) *ADAMTS13+(0.1384)*HEY1+(−0.5446)*SLC18A2+(−0.785)*EFCAB12+(0.2482)*TSPEAR+(0.0468)*CCBE1 +(0.0916)*ZDHHC11+(0.0764)*CCDC154+(0.1745)*HSPA1A+(0.1472)*ASPDH+(0.0558)*CCDC200). A heat map of prognostic gene expression was also generated, and 16 genes were selected. Gene expression profiles were integrated with clinical data to generate survival curves that stratified patients into high-risk and low-risk groups, followed by an analysis of survival outcomes within the validation dataset. We found that the low-risk subgroup had a longer OS than the high-risk group (Figure 2H). The 1-, 3-, and 5-year AUCs were 0.676, 0.668, and 0.672, respectively (Figure 2I).

Development and Validation of a Prognostic Nomogram of CRC

To explore the expression levels of the 16 key genes in normal tissues and tumor samples, we generated a violin plot. Among these genes, the mRNA expression of EFCAB12(EF-hand Calcium Binding Domain 12), ASPDH(Aspartate Dehydrogenase) and CCDC200(Coiled-Coil Domain Containing 200) showed no significant difference between normal and CRC tissues, while the mRNA expression of PANX2(Pannexin 2), AVPR1(Arginine Vasopressin Receptor 1), ULBP2(UL16 Binding Protein 2), HEY1(Hes Related Family bHLH Transcription Factor With YRPW Motif 1), SLC18A2(Solute Carrier Family 18 Member A2), TSPEAR(Thrombospondin Type Laminin G Domain And EAR Repeats), CCBEE1(Collagen And Calcium Binding EGF Domains 1), ZDHHC11(Zinc Finger DHHC-Type Containing 11), CCDC154(Coiled-Coil Domain Containing 154), and HSPA1A(Heat Shock Protein Family A Member 1A) were significantly elevated in CRC (Figure 3A). Further investigation revealed that these 16 key genes exhibit a strong and significant correlation with 24 immune-infiltrating cell types (Figure 3B).

In the next phase of the study, we screened out the prognostic features by cox analysis (Table 1). Moreover, we constructed a comprehensive clinicopathologic nomogram that integrated critical factors, including residual tumor extent, patient age (N stage), metastatic stage (M stage), and Clust risk. This predictive tool was designed to estimate overall survival (OS) at 1-year, 3-year, and 5-year intervals. The nomogram incorporated the risk score formula derived from the

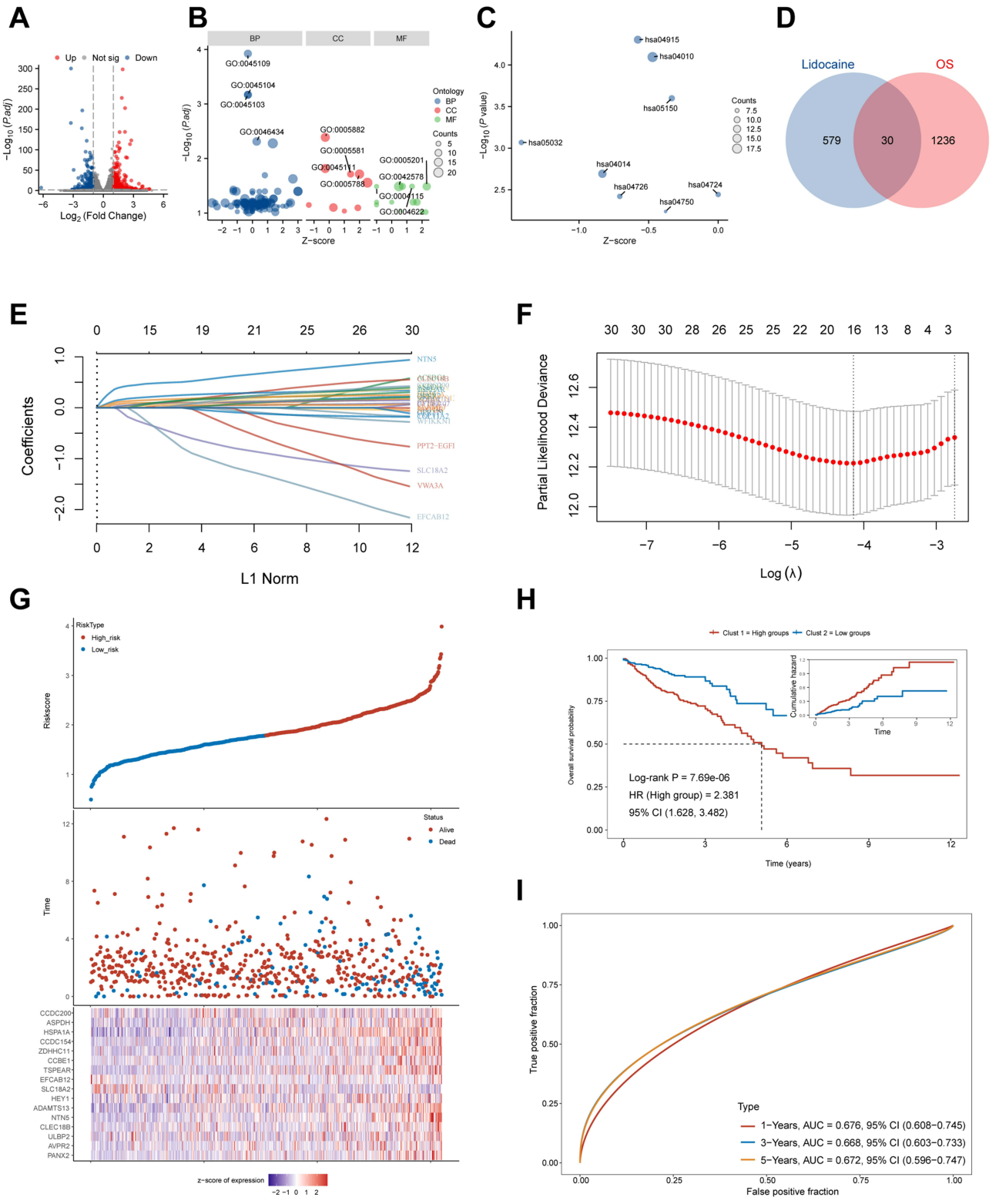

Figure 2 Screening and reduction analysis of targets at the intersection of treatment and prognosis. (**A**) Volcano plot showing an overview of the differential expression of Genes in HCT 116 cell line (n=3). (**B**) Gene Ontology (GO) enrichment analysis.(**C**) KEGG pathway enrichment analysis. (**D**)The Venn diagram of the overlapping of lidocaine targeted and OS genes (**E** and **F**) Lasso prognostic regression model.(**G**) Risk curve and heatmap of model gene expression in the high- and low-risk groups.(**H**) Survival curves in the TCGA database. (**I**) ROC curve to verify the accuracy of risk. *p < 0.05;**p < 0.01; ***p < 0.001.

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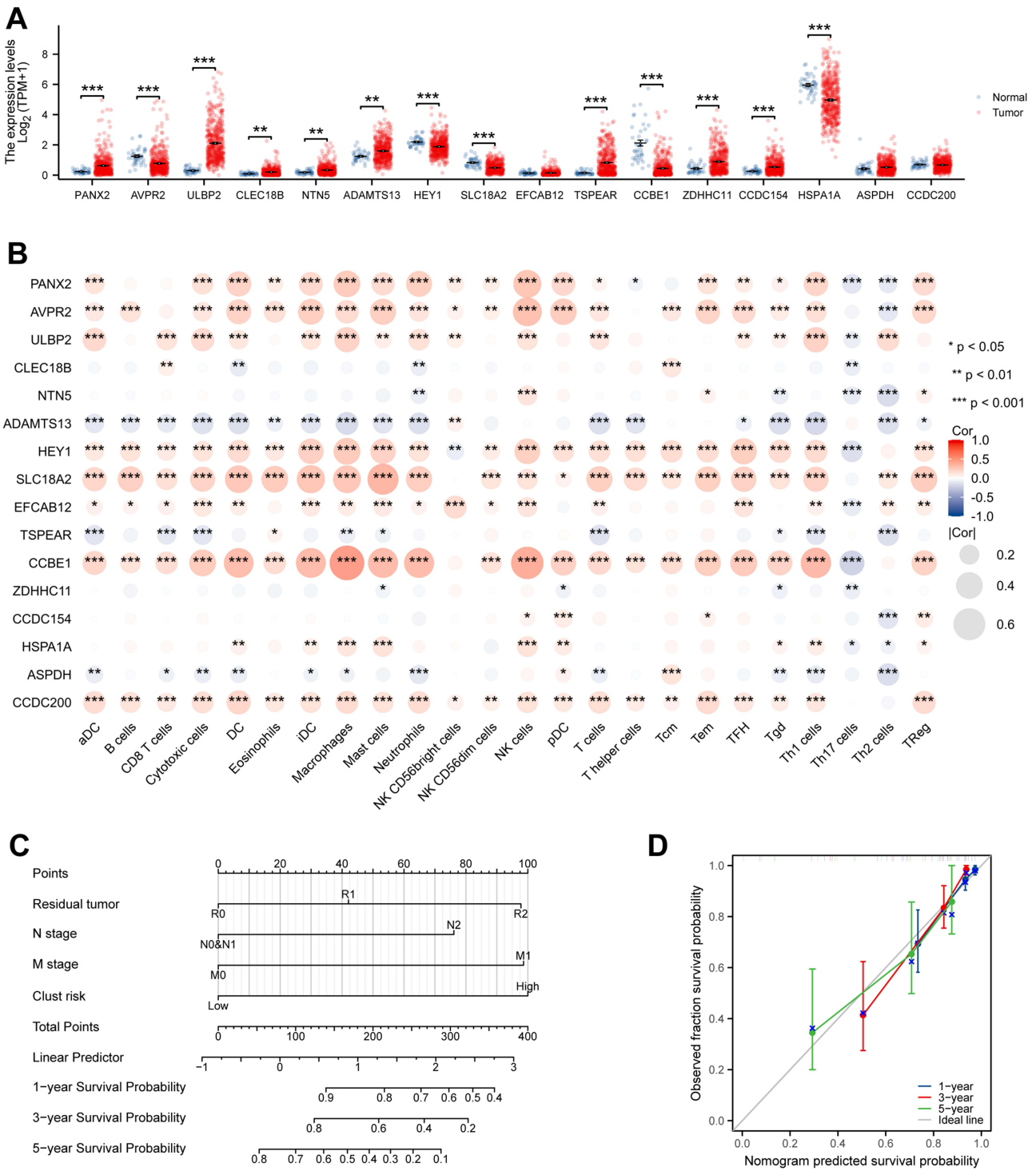

Figure 3 The relationship between the expression of prognostic genes and immune characteristics and the establishment of prognostic model. (**A**) Boxplots of the expression of 16 genes in normal and tumor groups. (**B**) The correlation between 16 genes and 24 immune infiltrating cells in CRC. (**C**) A nomogram to estimate the 1-, 3-, and 5-year survival probability. (**D**) Calibration plots of the nomogram. *p < 0.05;**p < 0.01; ***p < 0.001.

patient's clinical data and corresponding survival periods (Figure 3C). To assess the reliability and accuracy of the nomogram's predictions, a calibration plot was generated. This plot visually represented the agreement between predicted survival probabilities and actual outcomes, demonstrating a high degree of concordance and indicating the nomogram's strong predictive performance (Figure 3D).

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Table 1 Univariate and Multivariate Cox Regression Analyses of the Clinical Characteristics Associated with Overall Survival in Colorectal Cancer

Characteristics	Total(N)	HR (95% CI) Univariate Analysis	P value Univariate Analysis	HR (95% CI) Multivariate Analysis	P value Multivariate Analysis
Residual tumor	342				
R0	317	Reference		Reference	
R1	4	1.434 (0.335–6.134)	0.627	1.231 (0.287–5.284)	0.780
R2	21	7.012 (3.668–13.404)	< 0.001	2.345 (1.021–5.387)	0.045
T stage	437				
T1	11	Reference		Reference	
T2	75	0.367 (0.067–2.011)	0.248	0.805 (0.000 - Inf)	1.000
T3	300	1.272 (0.311–5.195)	0.738	73,577,456.8217 (0.000 - Inf)	0.999
T4	51	3.942 (0.919–16.905)	0.065	118,499,126.1475 (0.000 - Inf)	0.999
N stage	438				
N0&N1	360	Reference		Reference	
N2	78	3.508 (2.320–5.303)	< 0.001	1.951 (1.058–3.596)	0.032
M stage	384				
M0	323	Reference		Reference	
M1	61	4.780 (3.031–7.537)	< 0.001	2.244 (1.079–4.668)	0.030
Clust risk	438				
Low	230	Reference		Reference	
High	208	2.846 (1.850–4.377)	< 0.001	2.279 (1.257–4.130)	0.007

Kaplan-Meier Survival Analysis of 16 Genes

The survival impact of these 16 genes was further assessed using Kaplan-Meier (KM) survival curves for overall survival (OS). The KM curves revealed that patients with high expression levels of ASPDH, ZDHHC11, AVPR2, CCBE1, PANX2, CCDC154, TSPEAR, HSPA1A, NTN5, ULBP2, CCDC200, HEY1, and EFCAB12 had a reduced probability of survival. In contrast, patients with elevated SLC18A2 expression exhibited a more favorable survival rate (Figure 4). These findings further validate the relevance of the selected genes.

Through this systematic Kaplan-Meier analysis, we can not only identify potential prognostic markers but also provide a crucial foundation for subsequent clinical studies and treatment strategies.

Discussion

Colorectal cancer (CRC) remains one of the most common malignant tumors worldwide.[18,19] Despite advances in treatment, patients often face significant challenges in achieving optimal outcomes. Key challenges include the need for personalized treatment strategies tailored to the unique genetic and molecular characteristics of each patient's tumor.[8,20,21] For instance, alterations in the vascular endothelial growth factor (VEGF) system have emerged as potential biomarkers for guiding treatment decisions and improving prognostic accuracy.[22,23] Additionally, the treatment of metastatic CRC, particularly liver metastases,[24] poses significant clinical challenges. In locally advanced rectal cancer, the integration of neoadjuvant therapies, including chemotherapy and radiotherapy, has shown promise in improving surgical outcomes and reducing local recurrence rates.[25,26] However, optimizing the sequencing and combination of these therapies remains an area of ongoing research and debate. In the future, Western blot detection of apoptotic markers such as caspase-3 and Bcl-2 is needed to further verify the mechanism. This experimental concentration (250–366 μM) was higher than the plasma therapeutic concentration (4.3–21.5 μM), but close to the local tissue concentration (50–100 μM). Further research is needed to optimize the combination of traditional and new therapies. Multidisciplinary collaboration, such as oncologists, surgeons, and radiologists, is critical to developing an individualized approach. Local administration, such as intratumoral injection, needs to be explored in the future to reduce systemic toxicity while verifying in vivo efficacy.

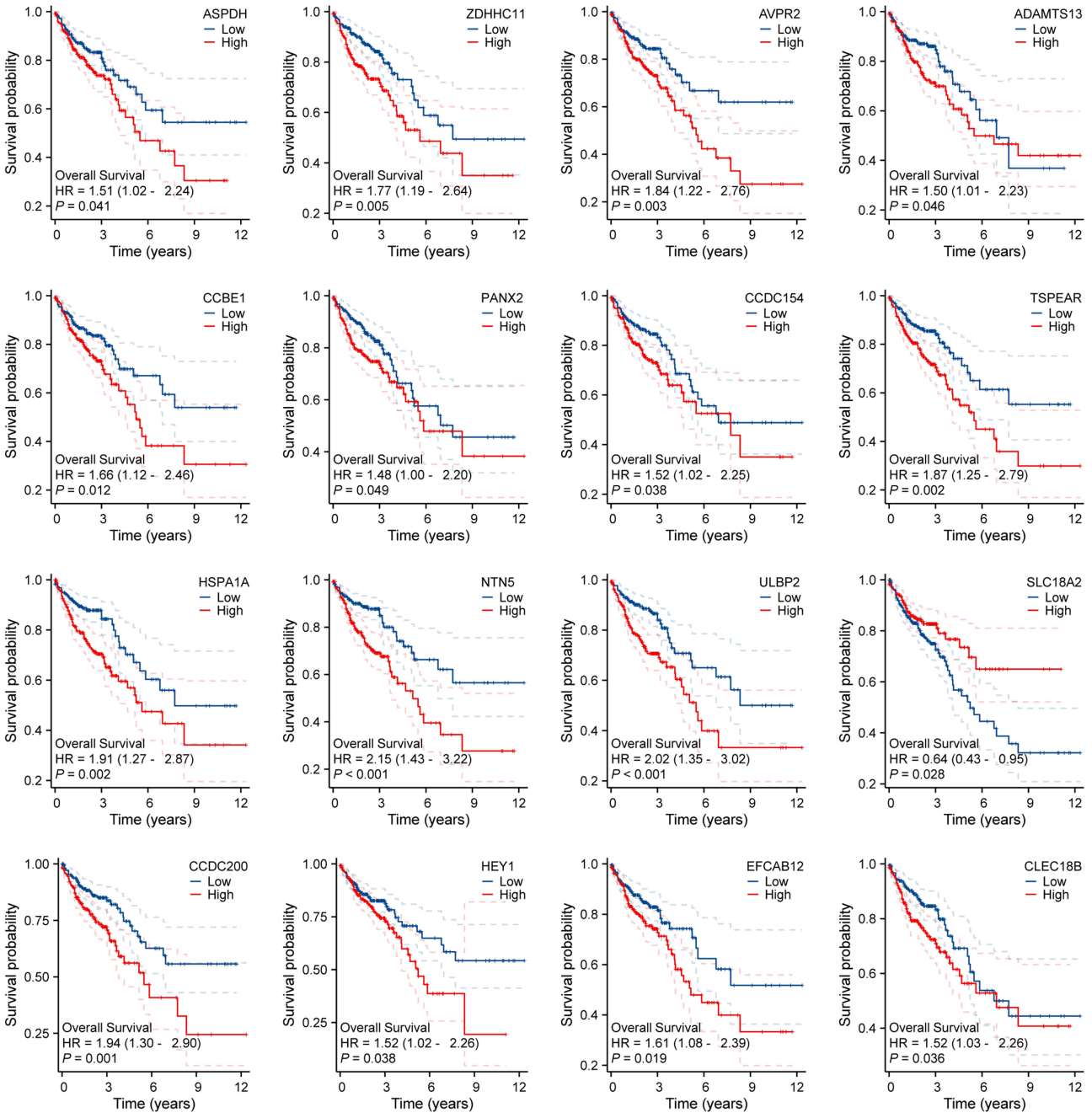

Figure 4 Kaplan-Meier survival analysis of OS based on expression levels of 16 genes in the training cohort.

The potential role of lidocaine in colorectal cancer has garnered widespread attention in recent years, particularly due to its multifaceted effects beyond its use as a local anesthetic.[27–29] Lidocaine has been shown to possess anticancer properties that may benefit colorectal cancer treatment. Recent studies suggest that lidocaine can act as a chemosensitizer, enhancing the efficacy of conventional chemotherapy drugs against resistant cancer cells. Studies have shown that lidocaine enhances the killing effect of 5-fluorouracil on drug-resistant cancer cells by inhibiting the ABC transporter.[30,31] This is particularly relevant given the challenges posed by drug resistance in cancer treatment. Some studies have indicated that local anesthetics like lidocaine can modulate inflammatory responses,[32,33] which are critical in cancer progression and metastasis. Interleukin-8 (IL-8), a pro-inflammatory cytokine, has been highlighted for its role in

colorectal cancer,[34] with elevated levels associated with tumor growth and metastasis. Lidocaine's potential to alter these inflammatory markers may further enhance its therapeutic role in colorectal cancer.[35,36]

Furthermore, the use of lidocaine as an anticancer agent aligns with broader drug repurposing strategies, which seek to utilize existing drugs for new therapeutic purposes. This approach not only accelerates the drug development process but also leverages the established safety profiles of these drugs. As clinical trials continue to explore lidocaine's efficacy in cancer treatment, its potential role in colorectal cancer remains a promising area of research.[37]

Conclusion

This study investigates the potential antitumor effects of lidocaine on colorectal cancer (CRC) through carefully designed cellular and molecular biology experiments, supplemented by bioinformatics analysis. Our results demonstrate that lidocaine significantly inhibits the proliferation, migration, and invasion of HCT 116 and SW480 CRC cell lines while inducing apoptosis, effectively suppressing tumor growth. This finding provides a new perspective on the application of lidocaine in cancer treatment and opens new avenues for CRC therapeutic strategies.

Using RNA sequencing and bioinformatics analysis, we identified clusters of differentially expressed genes in HCT 116 cells following lidocaine treatment. Through Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses, we elucidated the biological processes and signaling pathways associated with these genes, particularly the estrogen signaling pathway and the MAPK pathway, both of which play critical roles in cancer biology. These findings further reinforce lidocaine's antitumor effects in colorectal cancer.

Additionally, we developed a prognostic model based on 16 key genes, which was validated using clinical data to assess its efficacy in predicting CRC patient outcomes. This model not only supports personalized treatment strategies for CRC patients but also introduces a new tool for prognostic evaluation.

In conclusion, although the role of lidocaine in colorectal cancer is not yet fully understood, its effects on apoptosis, the tumor microenvironment, and resistance mechanisms offer exciting opportunities for future research. Further studies will elucidate these molecular mechanisms and explore the therapeutic potential of lidocaine in CRC treatment. Continued research in this area may lead to innovative therapeutic strategies to improve outcomes for colorectal cancer patients.

Data Sharing Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval

The institutional review board of Sir Run Run Hospital of Nanjing Medical University approved the study protocol.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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