## Contents

**Editorial**

1676  
Interleukin-1β: Friend or foe for gastrointestinal cancers  
Khawkhiaw K, Panaampon J, Imemkamon T, Saengboonmee C

1683  
Overcoming geographical and socioeconomic limitations in colorectal cancer screening  
Rozani S, Lykoudis PM

**Review**

1690  
Mechanisms of myeloid-derived suppressor cell-mediated immunosuppression in colorectal cancer and related therapies  
Nie SC, Jing YH, Lu L, Ren SS, Ji G, Xu HC

1705  
Impact of STAT-signaling pathway on cancer-associated fibroblasts in colorectal cancer and its role in immunosuppression  
Sánchez-Ramírez D, Mendoza-Rodríguez MG, Alemán OR, Candanedo-González FA, Rodríguez-Sosa M, Montesinos-Montesinos JJ, Salcedo M, Brito-Toledo I, Vaca-Paniagua F, Terrazas LI

**MiniReviews**

1725  
Advances in the study of gastric organoids as disease models  
Liu YY, Wu DK, Chen JB, Tang YM, Jiang F

**Original Article**

**Case Control Study**

1737  
Evaluation of the value of combined detection of tumor markers CA724, carcinoembryonic antigen, CA242, and CA19-9 in gastric cancer  
Zhou CM, Zhao SH

**Retrospective Cohort Study**

1745  
Different lymph node staging systems for predicting the prognosis of colorectal neuroendocrine neoplasms  
Zhang YY, Cai YW, Zhang X

1756  
Pancreatic neuroendocrine tumors: Are tumors smaller than 2 cm truly indolent?  

1763  
Albumin–bilirubin grade as a predictor of survival in hepatocellular carcinoma patients with thrombocytopenia  
Man ZR, Gong XK, Qu KL, Pang Q, Wu BQ
## Contents

### World Journal of Gastrointestinal Oncology

**Monthly Volume 16 Number 5 May 15, 2024**

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1773</td>
<td>TRIANGLE operation, combined with adequate adjuvant chemotherapy, can improve the prognosis of pancreatic head cancer: A retrospective study</td>
<td>Chen JH, Zhu LY, Cai ZW, Hu X, Ahmed AA, Ge JQ, Tang XY, Li CJ, Pu YL, Jiang CY</td>
</tr>
<tr>
<td>1787</td>
<td>Prognostic relevance of ventricular arrhythmias in surgical patients with gastrointestinal tumors</td>
<td>Xue JJ, Hu ST, Wang CC, Chen ZC, Cheng SY, Yu SQ, Peng HJ, Zhang YT, Zeng WJ</td>
</tr>
</tbody>
</table>

**Retrospective Study**

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1796</td>
<td>Diagnostic performance of dynamic contrast-enhanced magnetic resonance imaging parameters and serum tumor markers in rectal carcinoma prognosis</td>
<td>Mu RQ, Lv JW, Ma CY, Ma XH, Xing D, Ma HS</td>
</tr>
<tr>
<td>1808</td>
<td>Nomogram prediction of vessels encapsulating tumor clusters in small hepatocellular carcinoma ≤ 3 cm based on enhanced magnetic resonance imaging</td>
<td>Chen HL, He RL, Gu MT, Zhao XY, Song KR, Zou WJ, Jia NY, Liu WM</td>
</tr>
<tr>
<td>1821</td>
<td>Percutaneous transhepatic cholangioscopy-assisted biliary polypectomy for local palliative treatment of intraductal papillary neoplasm of the bile duct</td>
<td>Ren X, Qu YP, Zhu CL, Xu XH, Jiang H, Lu YX, Xue HP</td>
</tr>
<tr>
<td>1849</td>
<td>Magnetic resonance imaging-based lymph node radiomics for predicting the metastasis of evaluable lymph nodes in rectal cancer</td>
<td>Ye YX, Yang L, Kang Z, Wang MQ, Xie XD, Lou KX, Bao J, Du M, Li ZX</td>
</tr>
<tr>
<td>1861</td>
<td>Is sarcopenia effective on survival in patients with metastatic gastric cancer?</td>
<td>Dogan O, Sahinli H, Duzkopru Y, Akdag T, Kocanoglu A</td>
</tr>
<tr>
<td>1869</td>
<td>Clinical outcome and prognostic factors of T4N0M0 colon cancer after R0 resection: A retrospective study</td>
<td>Liu B, Zhang ZX, Nie XY, Sun WL, Yan YJ, Fu WH</td>
</tr>
</tbody>
</table>

**Observational Study**

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1878</td>
<td>Correlation of tumor-associated macrophage density and proportion of M2 subtypes with the pathological stage of colorectal cancer</td>
<td>Fazal F, Khan MA, Shawana S, Rashid R, Mubarak M</td>
</tr>
</tbody>
</table>

**Clinical and Translational Research**

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1890</td>
<td>SERPINH1 promoted the proliferation and metastasis of colorectal cancer by activating PI3K/Akt/mTOR signaling pathway</td>
<td>Jin XS, Chen LX, Ji TT, Li RZ</td>
</tr>
<tr>
<td>1908</td>
<td>Four centrosome-related genes to predict the prognosis and drug sensitivity of patients with colon cancer</td>
<td>Wang HY, Diao Y, Tan PZ, Liang H</td>
</tr>
<tr>
<td>Page</td>
<td>Title</td>
<td>Authors</td>
</tr>
<tr>
<td>------</td>
<td>-----------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>1925</td>
<td>METTL5 promotes gastric cancer progression via sphingomyelin metabolism</td>
<td>Zhang YQ, Li J, Qin Z, Li DM, Ye FZ, Bei SH, Zhang XH, Feng L</td>
</tr>
<tr>
<td>1995</td>
<td>Casual associations between blood metabolites and colon cancer</td>
<td>Hu KY, Cheng YQ, Shi ZL, Ren FP, Xiao GF</td>
</tr>
</tbody>
</table>

**Basic Study**

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>METTL5 promotes cell proliferation, invasion, and migration by up-regulating Toll-like receptor 8 expression in colorectal cancer</td>
<td>Kong LS, Tao R, Li YF, Wang WB, Zhao X</td>
</tr>
<tr>
<td>2018</td>
<td>Predictive model using four ferroptosis-related genes accurately predicts gastric cancer prognosis</td>
<td>Wang L, Gong WH</td>
</tr>
<tr>
<td>2060</td>
<td>Epigenetic silencing schlafen-11 sensitizes esophageal cancer to ATM inhibitor</td>
<td>Zhou J, Zhang MY, Gao AA, Zhu C, He T, Herman JG, Guo MZ</td>
</tr>
<tr>
<td>2074</td>
<td>Transglutaminase 2 serves as a pathogenic hub gene of KRAS mutant colon cancer based on integrated analysis</td>
<td>Peng WB, Li YP, Zeng Y, Chen K</td>
</tr>
<tr>
<td>2091</td>
<td>Plexin domain-containing 1 may be a biomarker of poor prognosis in hepatocellular carcinoma patients, may mediate immune evasion</td>
<td>Tang MY, Shen X, Yuan RS, Li HY, Li XW, Jing YM, Zhang Y, Shen HH, Wang ZS, Zhou L, Yang YC, Wen HX, Su F</td>
</tr>
<tr>
<td>2123</td>
<td>MiRNA-145-5p inhibits gastric cancer progression via the serpin family E member 1- extracellular signal-regulated kinase-1/2 axis</td>
<td>Bai HX, Qiu XM, Xu CH, Guo JQ</td>
</tr>
</tbody>
</table>

**SYSTEMATIC REVIEWS**

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>2141</td>
<td>Systematic review of risk factors, prognosis, and management of colorectal signet-ring cell carcinoma</td>
<td>Nuytens F, Drubay V, Eveno C, Renaud F, Piessen G</td>
</tr>
</tbody>
</table>
## Contents

### META-ANALYSIS

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>2159</td>
<td>Loss of heterozygosity for chromosomes 16q in Wilms tumors predicts outcomes: A meta-analysis</td>
<td>Song YH, Li WL, Yang Z, Gao Y, Feng ZP</td>
</tr>
<tr>
<td>2168</td>
<td>Association of complement components with risk of colorectal cancer: A systematic review and meta-analysis</td>
<td>Zhu XL, Zhang L, Qi SX</td>
</tr>
</tbody>
</table>

### SCIENTOMETRICS

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>2181</td>
<td>Mapping the intellectual structure and emerging trends for the application of nanomaterials in gastric cancer: A bibliometric study</td>
<td>Liu BN, Gao XL, Piao Y</td>
</tr>
</tbody>
</table>

### CASE REPORT

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>2225</td>
<td>Multidisciplinary comprehensive treatment of massive hepatocellular carcinoma with hemorrhage: A case report and review of literature</td>
<td>Kou XS, Li FF, Meng Y, Zhao JM, Liu SF, Zhang L</td>
</tr>
<tr>
<td>2241</td>
<td>Hepatocellular carcinoma presenting as an extrahepatic mass: A case report and review of literature</td>
<td>Wu WK, Patel K, Padmanabhan C, Idrees K</td>
</tr>
<tr>
<td>2253</td>
<td>Undifferentiated high-grade pleomorphic sarcoma of the common bile duct: A case report and review of literature</td>
<td>Zheng LP, Shen WY, Hu CD, Wang CH, Chen XJ, Wang J, Shen YY</td>
</tr>
</tbody>
</table>

### LETTER TO THE EDITOR

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>2261</td>
<td>Hemostatic radiotherapy for bleeding gastrointestinal tumors</td>
<td>Rao V, Singh S, Zade B</td>
</tr>
</tbody>
</table>
ABOUT COVER

Peer Reviewer of *World Journal of Gastrointestinal Oncology*, Andreia Albuquerque, MD, PhD, Gastroenterologist, Professor, Research Scientist, Precancerous Lesions and Early Cancer Management Research Group RISE@CI-IPO (Health Research Network), Portuguese Oncology Institute of Porto (IPO-Porto), Porto 4200-072, Portugal. a.albuquerque.dias@gmail.com

AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Oncology* (*WJGO*, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

*WJGO* mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, etc.

INDEXING/ABSTRACTING

The *WJGO* is now abstracted and indexed in PubMed, PubMed Central, Science Citation Index Expanded (SCIE, also known as SciSearch®), Journal Citation Reports/Science Edition, Scopus, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2023 edition of Journal Citation Reports® cites the 2022 impact factor (IF) for *WJGO* as 3.0; IF without journal self cites: 2.9; 5-year IF: 3.0; Journal Citation Indicator: 0.49; Ranking: 157 among 241 journals in oncology; Quartile category: Q3; Ranking: 58 among 93 journals in gastroenterology and hepatology; and Quartile category: Q3. The *WJGO*’s CiteScore for 2022 is 4.1 and Scopus CiteScore rank 2022: Gastroenterology is 71/149; Oncology is 197/366.

RESPONSIBLE EDITORS FOR THIS ISSUE

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Basic Study

MiRNA-145-5p inhibits gastric cancer progression via the serpin family E member 1- extracellular signal-regulated kinase-1/2 axis

Hong-Xia Bai, Xue-Mei Qiu, Chun-Hong Xu, Jian-Qiang Guo

Abstract

BACKGROUND

MicroRNAs (miRNAs) regulate gene expression and play a critical role in cancer physiology. However, there is still a limited understanding of the function and regulatory mechanism of miRNAs in gastric cancer (GC).

AIM

To investigate the role and molecular mechanism of miRNA-145-5p (miR145-5p) in the progression of GC.

METHODS

Real-time polymerase chain reaction (RT-PCR) was used to detect miRNA expression in human GC tissues and cells. The ability of cancer cells to migrate and invade was assessed using wound-healing and transwell assays, respectively. Cell proliferation was measured using cell counting kit-8 and colony formation assays, and apoptosis was evaluated using flow cytometry. Expression of the epithelial-mesenchymal transition (EMT)-associated protein was determined by Western blot. Targets of miR-145-5p were predicted using bioinformatics analysis and verified using a dual-luciferase reporter system. Serpin family E member 1 (SERPINE1) expression in GC tissues and cells was evaluated using RT-PCR and immunohistochemical staining. The correlation between SERPINE1 expression and overall patient survival was determined using Kaplan-Meier plot analysis. The association between SERPINE1 and GC progression was also tested. A rescue experiment of SERPINE1 overexpression was conducted to verify the relationship
between this protein and miR-145-5p. The mechanism by which miR-145-5p influences GC progression was further explored by assessing tumor formation in nude mice.

RESULTS
GC tissues and cells had reduced miR-145-5p expression and SERPINE1 was identified as a direct target of this miRNA. Overexpression of miR-145-5p was associated with decreased GC cell proliferation, invasion, migration, and EMT, and these effects were reversed by forcing SERPINE1 expression. Kaplan-Meier plot analysis revealed that patients with higher SERPINE1 expression had a shorter survival rate than those with lower SERPINE1 expression. Nude mouse tumorigenesis experiments confirmed that miR-145-5p targets SERPINE1 to regulate extracellular signal-regulated kinase-1/2 (ERK1/2).

CONCLUSION
This study found that miR-145-5p inhibits tumor progression and is expressed in lower amounts in patients with GC. MiR-145-5p was found to affect GC cell proliferation, migration, and invasion by negatively regulating SERPINE1 levels and controlling the ERK1/2 pathway.

Key Words: Gastric cancer; MicroRNA-145-5p; Serpin family E member 1; Epithelial-mesenchymal transition; Proliferation; Extracellular signal-regulated kinase-1/2

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UTR. However, the exact role of miR-145-5p in GC remains poorly understood. In this study, we used real-time polymerase chain reaction (RT-PCR), transwell assay, colony formation assay, Western blot, dual-luciferase reporter system, nude mice model, and many other methods to find that the expression of miR-145-5p was negatively related to GC progression by targeting serpin family E member 1 (SERPINE1) through signal-regulated kinase-1/2 (ERK1/2) pathway.

**MATERIALS AND METHODS**

**Bioinformatics analysis**

GC miRNA and mRNA expression data were acquired from The Cancer Genome Atlas (TCGA) database (https://portal.gdc.cancer.gov/). The “edgeR” package was used to obtain the differentially expressed miRNAs and mRNAs and a boxplot was constructed and confirmed as the research object. Two databases (TargetScan and miRDB) were employed to predict the downstream target miRNAs of miR-145-5p. A Venn diagram was created to find the potential target mRNA.

**Cell lines and cell culture**

The human GC cell lines (BGC-823, MGC-803, HGC-27, and SGC-7901) and the immortalized normal gastric mucosal cell line (GES-1) were purchased from the Cell Bank of the Chinese Academy of Sciences (CAS, China). All cell lines were cultured in RPMI-1640 medium (MACGENE, China) supplemented with 10% fetal bovine serum (Excell Bio, China), 100 μg/mL streptomycin, and 100 U/mL Penicillin and incubated at 37 °C and 5% CO₂. When the cells reached a confluency of 80%-90%, they were passaged and reseeded at an appropriate density.

**Cell transfection**

For functional assays, miR-145-5p mimic (mimic), miR-145-5p inhibitor (inhibitor), NC for miR-145-5p mimic (mimic-NC), and NC for miR-145-5p inhibitor (inhibitor-NC) were synthesized and purified by Ribobio (China). Transfections were performed using Lipofectamine2000 (Invitrogen, United States) following the provided guidelines: When the cells reached the logarithmic growth phase, trypLE was used to digest the cells. The cells were then centrifuged, resuspended, and counted on a 6-well plate (with a fusion degree of about 80%) during cell transfection. The mixed siRNA (100 nM) and an appropriate amount of Lipofectamine2000 dissolved in serum free Opti MEM I was added to the plate. After transfection, the culture medium was replaced after culturing the cells in a CO₂ incubator at 37 °C for 4-6 h. The cells were incubated for 48 h before proceeding with additional experiments.

To verify the role of SERPINE1 in GC, the SGC-7901 and HGC-27 cells were transfected with lentivirus (sourced from Genomediecc), China. The cells were classified into two groups: Overexpressed SERPINE1 (OE) and control (OE-NC). Both the HGC27 and SGC7901 cells were cultivated overnight in 6-well plates. After reaching 40%-50% confluence, lentiviral infection was introduced. Stable transfectants were subsequently selected using 1 μg/mL puromycin screening. The expression of SERPINE1 in stably transfected cell lines was assessed using western blotting and q-PCR.

For the rescue experiment, HGC27 and SGC7901 cells were stably transfected with miR-145-5p-mimic (mimic) and miR-145-5p-mimic-NC (mimic-NC) and divided into four groups: Mimic-NC + OE-NC, mimic + OE-NC, mimic-NC + OE, and mimic + OE.

**RNA extraction and real-time quantitative PCR**

TRNzol reagent (Tiangen Biotech, China) was used for total RNA extraction and then reverse-transcribed into cDNA using a miRNA 1° Strand cDNA Synthesis Kit (Vazyme Biotech Co., Ltd, China). The real-time quantitative PCR (qRT-PCR) process was carried out using SYBR Green (Tiangen Biotech Co, Ltd, China) according to a specific thermal cycling protocol. U6 and actin served as endogenous controls, and the target miRNA and mRNA relative expression levels were calculated using the 2⁻ΔΔCt method. The primers used in this study were synthesized by Beijing hanghang Changsheng Biotech. Co., Ltd (Table 1).

**Western blotting**

Total protein was isolated from the cells using 1 x sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) Sample Loading Buffer (Beyotime Biotechnology, China). A BCA Protein Assay Kit (Beyotime Biotechnology, China) was used to determine the concentration of the protein samples, and the samples were quantified at different concentrations. The proteins were then boiled at 100°C for 10 min with 100 μL of loading buffer (Beyotime Biotechnology, China) and separated by SDS-PAGE at 120 V. After electrophoresis, the proteins were transferred onto PVDF membranes and blocked using 5% BSA/TBST for 60 min. The primary rabbit polyclonal antibodies, SERPINE1 (Proteintech, United States), α-smooth muscle actin (α-SMA) (Proteintech, United States), β-catenin (Proteintech, United States), vimentin (HuBio, China), ERK1/2 (HuBio, China), phosphorylation extracellular signal-regulated kinase1/2 (p-ERK1/2) (HuBio, China) and actin (ZSGB-BIO, China), and the mouse monoclonal antibody E-cad (HuBio, China), were added to the membranes and incubated overnight at 4 °C. Secondary goat anti-rabbit IgG or goat anti-mouse IgG (ZSGB-BIO, China) antibodies were then added and the membrane was incubated at room temperature for 1 h and then washed three times with TBST buffer for 10 min. The Immobilon Western Chemilum HRP Substrate (WBKLS0500, Millipore, United States) was used to visualize the protein bands, and Image Pro Plus 6.0 (Media Cybernetics, United States) software was employed to analyze the relative protein levels.
Table 1 Primer sequences used in this study

<table>
<thead>
<tr>
<th>Gene</th>
<th>Primer sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>miR-145-5p</td>
<td>F: 5′-GCCTTGGCAATGTAGAACT-3′</td>
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<tr>
<td></td>
<td>R: 5′-AGTGCAGCTGAAAGTATT-3′</td>
</tr>
<tr>
<td>U6</td>
<td>F: 5′-CCAGGCAAGGTTCCGAGTA-3′</td>
</tr>
<tr>
<td>SERPINE1</td>
<td>F: 5′-GGATGAGAAAACCAGTTCG-3′</td>
</tr>
<tr>
<td>Actin</td>
<td>F: 5′-TTCAGCAGATTTCC-3′</td>
</tr>
</tbody>
</table>

Immunohistochemistry staining assay

Tumor tissue from human or nude mice was fixed with 4% formaldehyde, dehydrated, embedded in paraffin, and cut into 4 μm thick tissue sections. After heating at 60 °C for 1 h, the slices were dewaxed and rehydrated with a concentration gradient of alcohol (100, 95, 90, 80, and 70%). The tissue sections were boiled in 10 mmol/L sodium citrate buffer (pH 6.0) at a high temperature to recover the antigens, and incubated for 20 min with 3% hydrogen peroxide to block endogenous peroxidase activity. BSA (5%) was added to the sections and sealed for 30 min. The slices were incubated overnight with primary anti-SERPINE1 (Proteintech, United States, 1:500) and anti-Ki67 (Proteintech, United States, 1:10000) antibodies at 4 °C. The tissue was then incubated with a secondary antibody and observed under a microscope. The slices were then washed with tap water to stop the coloration. Harris hematoxylin (BOSTER, AR1108) was used to restain the samples for 5 min (the time was controlled by the degree of staining). The samples were then washed in tap water, differentiated with 1% hydrochloric acid alcohol for a few seconds, and rinsed in tap water. When the ammonia water was blue, the samples were rinsed in running water, dehydrated, and sealed. The images were observed and captured using a fluorescence microscope.

Dual-luciferase reporter gene assay

A Dual-Luciferase Reporter Gene Assay was conducted to predict the binding site of miR-145-5p and SERPINE1 3'-UTR. Wild-type and mutant SERPINE1 3'-UTR fragments were synthesized and cloned into the pmirGLO plasmid. The amplified sequences of the wild type 3'UTR of SERPINE1 (WT-3'UTR) were cloned into the pmirGLO vectors (Promega Corp., WI, United States) for the construction of luciferase Wt-SERPINE1 vectors and mutant vectors (luciferase Mut-SERPINE1) were synthesized by Sangon Biotech (China). MiR-145-5p mimic and NC were co-transfected into 293T cells with Wt-SERPINE1 or Mut-SERPINE1 (SCSP-502, National Collection of Authenticated Cell Cultures, China), respectively. After 48 h, Firefly and Renilla luciferase activities were measured using the Varioskan LUX Multi-function enzyme labeling instrument (Thermo Scientific, United States).

Cell growth assay

GC cell proliferation was measured using a cell counting kit-8 (CCK-8), Meilunbio, China. GC cells at a density of 5 × 10^3 cells/well were suspended in 100 μL and incubated in 96-well plates at 5% CO₂ and 37 °C for 48 h. CCK-8 reagent (10 μL) was introduced into each well for a 4-h incubation. Absorbance values were recorded at 450 nm.

Cells were dispensed into 6-well plates at a density of 1000 cells/well to assess colony formation. After 10 d, the colonies were preserved using methanol and stained with 0.1% crystal violet alcohol solvent (G1014-50ML, Servicebio, China) for 15 min. Images of the stained colonies were obtained and their numbers were determined.

Flow cytometry

Flow cytometry was performed according to the Annexin V-FITC/PI apoptosis kit (Multi Sciences, China) instructions. To test the samples, 5 × 10^5 cells, including those in the culture supernatant, were collected by centrifuging with pre-cooled phosphate-buffered saline (PBS) at 4 °C and 1500 rpm for 5 min. Annexin V-FITC (5 μL) and 10 μL PI were added to each tube, mixed gently, and incubated in the dark at room temperature for 5 min. A CytoFLEX (BECKMAN, United States) was used to analyze the proportion of apoptotic cells in each sample. Annexin V-FITC was detected using the FITC detection channel (Ex = 488 nm; Em = 530 nm), and PI was detected using the PI detection channel (Ex = 535 nm; Em = 615 nm).

Invasion assay

A 24-well Transwell BD Matrigel system (FN, Corning, Costar, China) with an 8 μm pore size was used to measure cellular invasion. Approximately 7.5 × 10^4 cells were added to the upper chamber pre-coated with a Matrigel matrix (Yes Service Biotech, China), while the lower chamber was filled with RPMI-1640 medium containing 10% FBS to act as an
MiR-145-5p is downregulated in GC tissues and cells

This study used the “edgeR” package to identify DEMiRNAs in TCGA-CESC data. The findings revealed that miR-145-5p was significantly downregulated in tumor tissues (Figure 1A). RT-PCR was then used to evaluate miR-145-5p expression in 30 paired samples of fresh GC tissues and their corresponding non-tumor tissues (P < 0.001). MiR-145-5p was expressed at much lower levels in GC tissues than their non-tumor counterparts (Figure 1B). Moreover, when compared with the immortalized normal gastric mucosal cell line, miR-145-5p expression was markedly lower in MGC803 (P < 0.05), HGC27 (P < 0.001), BGC823 (P < 0.01), and SGC7901 (P < 0.001) cell lines (Figure 1C). Since miR-145-5p expression was lowest in SGC7901 cells and highest in HGC27 cells, these cell lines were selected for the gain-of-function and loss-of-function assays, respectively.

MiR145-5p inhibits GC cell proliferation and promotes apoptosis

MiR-145-5p downregulation in GC cells suggested that it may play an inhibitory role in this disease. Thus, its mimics and inhibitors were introduced into GC cells (Figure 2A). As expected, miR-145-5p expression was higher in the mimic group (P < 0.01) and lower in the inhibitor group (P < 0.01) (Figure 2A). CCK-8 and colony formation experiments were used to determine if miR-145-5p could regulate GC proliferation. Cell viability was higher in the miR-145-5p inhibition group than in the inhibitor-NC group (P < 0.001) (Figure 2B), and the number of clones formed was also higher (P < 0.001) (Figure 2C). The miR145-5p-mimic group had less cell proliferation than the mimic group (P < 0.001) (Figure 2B), and a fewer number of clones formed (P < 0.01) (Figure 2C).

Flow cytometry was used to measure HGC27 and SGC7901 cell apoptosis after transfection. The number of apoptotic cells was higher in the miR-145-5p mimic group than in the mimic-NC group (P < 0.05). Furthermore, the number of apoptotic cells was lower in the miR-145-5p inhibitor group than in the inhibitor-NC group (P < 0.01) (Figure 2D).
SERPINE1 is a direct target of miR-145-5p

The bioinformatics tool, TargetScan, was used to predict the binding sites of miR-145-5p and SERPINE1 3’-UTR and better understand the molecular mechanism of miR-145-5p action (Figure 4A). Furthermore, to determine whether miR-145-5p directly regulates SERPINE1, SERPINE1 3’-UTR fragments (both wild-type, WT-LZTS1 3’-UTR, and mutated, Mut-LZTS1 3’-UTR) were cloned into a dual luciferase reporter vector (pmirGLO plasmid) and a luciferase reporter assay was conducted (Figure 4B). Co-transfection of 293T cells with miR-145-5p mimic and a vector carrying WT-SERPINE1 3’-UTR led to a significant reduction in luciferase activity (P < 0.001) (Figure 4C). These results suggest that miR-145-5p negatively regulates SERPINE1 expression by directly targeting its 3’-UTR, confirming the predictive findings of TargetScan.

SERPINE1 is upregulated in GC tissues and cells

TargetScan and miRDB bioinformatics tools were used to predict the miR-145-5p target gene and better characterize how this miRNA regulates the biological behavior of GC. A Venn diagram was created to visualize the results (Figure 5A). SERPINE1 was identified as a potential target gene of miR-145-5p. This gene is associated with malignant biological behaviors including tumor cell proliferation, invasion, metastasis, and apoptosis, as well as poor clinical prognosis[26-28]. Assessment of TCGA data confirmed that SERPINE1 expression was significantly higher in tumors than in normal tissues (Figure 5B).

Kaplan-Meier plot analysis revealed that patients with high SERPINE1 expression had a shorter survival rate than those with the low SERPINE1 expression (Figure 5C). Both SERPINE1 mRNA and protein expression were also significantly higher in GC tissue (P < 0.0001) as well as the HGC27 (P < 0.01) and SGC7901 (P < 0.01) cell lines (Figure 5D). Furthermore, SERPINE1 expression was significantly lower in cells in the mimic group (P < 0.01) and increased in cells in the inhibitor group (P < 0.01) (Figure 5E). These findings suggest that there is a negative correlation between miR-145-5p and SERPINE1 in GC.

SERPINE1 promotes GC cell proliferation, invasion, and migration and inhibits apoptosis

The SGC7901 cell line was used to stably OE and OE-NC-SERPINE1 (OE-NC) for subsequent experiments. The transfection efficiency of SERPINE1 was assessed using qRT-PCR (P < 0.01) and Western blotting (Figure 6A). The CCK-8 (P < 0.001) (Figure 6B) and colony formation assay (P < 0.01) data (Figure 6C) corroborated that the overexpression of SERPINE1 enhances SGC7901 cell proliferation. Meanwhile, transwell invasion (P < 0.01) (Figure 6D) and wound healing

Figure 1 MicroRNA-145-5p is poorly expressed in gastric cancer tissues and cells. A: Box diagram showing the differential expression of microRNA-145-5p (miR-145-5p) in normal and tumor data from The Cancer Genome Atlas-STAD. B: Differentially expressed miR-145-5p in the normal and tumor groups; C: MiR-145-5p expression in four gastric cancer (GC) cell lines, MGC803, HGC27, BGC823, SGC7901, and the normal GC line, GES-1. *P < 0.05; **P < 0.01; ***P < 0.001.

MiR-145-5p inhibits GC cell invasion, migration, and epithelial-mesenchymal transition transformation

The wound healing assay results indicated that the up-regulation of miR-145-5p suppressed SGC7901 cell migration (P < 0.01). Conversely, the down-regulation of miR-145-5p expression significantly enhanced HGC27 cell migration (P < 0.001) (Figure 3A). The transwell assays showed similar results, with a significantly lower number of invasive cells in the miR-145-5p mimic group than in the mimic-NC group (P < 0.05). Moreover, the number of invasive cells in the miR-145-5p inhibitor group was higher than in the inhibitor-NC group (P < 0.01) (Figure 3B).

To explore whether miR-145-5p could reverse the epithelial-mesenchymal transition (EMT) phenotype, the expression of EMT-related marker proteins (E-cadherin, β-catenin, Vimentin, and α-SMA) was assessed in HGC27 and SGC7901 cells. The upregulation of miR-145-5p significantly increased the expression of E-cadherin and decreased the expression of β-catenin, Vimentin, and α-SMA. Meanwhile, reducing the expression of miR-145-5p had the opposite effect (Figure 3C).

These findings suggest that miR-145-5p acts as a tumor suppressor and can reverse the EMT phenotype, which in turn inhibits GC cell proliferation, invasion, and metastasis.
assays \((P < 0.05)\) (Figure 6E) performed on the stably transfected cells indicated that \(\text{SERPINE1}\) overexpression stimulates GC cell invasion and metastasis. Flow cytometric analysis revealed that \(\text{SERPINE1}\) overexpression inhibits SGC7901 cell apoptosis \((P < 0.001)\) (Figure 6F). These findings suggest that \(\text{SERPINE1}\) functions as an oncogene in GC cells.
MiR-145-5p inhibits GC progression

**Figure 3** MicroRNA-145-5p inhibits gastric cancer cell migration, invasion, and epithelial-mesenchymal transition. A: HGC27 and SGC7901 cell migration; scale bar = 100 μm; B: HGC27 and SGC7901 cell invasion; scale bar = 100 μm; C: Epithelial-mesenchymal transition-related marker protein (E-cadherin, β-catenin, vimentin, and α-smooth muscle actin) expression in HGC27 and SGC7901 cells. *P < 0.05; **P < 0.01; ***P < 0.001.

**SERPINE1 reverses miR-145-5p-mediated cell proliferation, invasion, metastasis, EMT, and apoptosis**

Rescue experiments were conducted to further elucidate the effects of SERPINE1 on miR-145-5p-mediated cell proliferation, apoptosis, invasion, metastasis, and EMT. SGC7901 cells were cotransfected with OE-SERPINE1/OE-NC and miR-145-5p mimic/miR-145-5p mimic NC. Western blotting revealed that the miR-145-5p mimic and OE-SERPINE1+ miR-145-5p mimic groups had lower SERPINE1 protein expression than the miR-145-5p mimic NC and OE-NC+ miR-145-5p mimic groups, respectively (Figure 7A). Overexpression of SERPINE1 in SGC7901 cells partially counteracted the inhibitory effect of miR-145-5p on cell proliferation (P < 0.001) (Figure 7B and C), migration (Figure 7D), invasion (Figure 7E), and EMT (Figure 7F). SERPINE1 also partially reversed miR145-5p-induced apoptosis (Figure 7G). These findings suggest that miR145-5p negatively regulates SERPINE1 in GC, thereby facilitating cell apoptosis, inhibiting cell proliferation, invasion, and metastasis, and reversing EMT.

**SERPINE1 promotes cell proliferation and EMT transformation through the ERK1/2 pathway**

The salvage experiment assessed ERK1/2 and p-ERK1/2 protein expression in the four groups. While miR145-5p and SERPINE1 did not affect ERK1/2 protein expression, miR-145-5p overexpression suppressed p-ERK1/2 expression. Meanwhile, elevated SERPINE1 levels partially counteracted the effect of miR-145-5p (Figure 8A).

To further verify this mechanism, a GC tumor model was established in nude mice. All nude mice were evenly distributed into three groups (NC, OE, and OE + PD98059). Tumor tissues in the mice that overexpressed SERPINE1 (OE group) were heavier and larger in volume than those in the NC group. In contrast, nude mice that received PD98059, an ERK1/2 signal inhibitor, via intraperitoneal administration, had reduced tumor weight (P < 0.01) and volume (P < 0.001).
Figure 4. Serpin family E member 1 is a target of microRNA-145-5p. A: miRNA-145-5p and serpin family E member 1 (SERPINE1) 3'-UTR binding sites were predicted using TargetScan; B: WT-SERPINE1 and MUT-SERPINE1 sequences; C: Relative luciferase activity of 293T cells transfected with either WT-SERPINE1 or MUT-SERPINE1. *P < 0.001.

( Figures 8B and C). Immunohistochemical analysis of the tumor tissue revealed that Ki67 was highly expressed in the group with SERPINE1 overexpression. However, its expression was diminished in the tissues from the OE+PD98059 group (Figure 8D). Western blot results revealed that while SERPINE1 overexpression inhibited E-cadherin expression, boosted vimentin expression, induced EMT, and increased ERK1/2 phosphorylation, it had no impact on total ERK1/2 expression. In contrast, PD98059-induced blockage of the ERK1/2 pathway increased E-cadherin and reduced vimentin expression (Figure 8E). In summary, these results indicate that miR-145-5p negatively regulates SERPINE1, inhibiting ERK1/2 signaling, and ultimately suppressing GC proliferation and EMT.

DISCUSSION

GC is a commonly occurring cancer[29,30] that remains a serious threat to human health, primarily due to its late diagnosis, rapid progression, and high rates of metastasis and postoperative recurrence. The in vivo and in vitro findings of this study indicate that miR-145-5p inhibits GC formation. The results also show that miR-145-5p targets SERPINE1, suggesting that this miRNA inhibits GC development by suppressing the miR-145-5p/SERPINE1/ERK1/2 axis.

Several studies have confirmed that miRNAs, which can function as either proto-oncogenes or tumor suppressor genes, play a pivotal role in the biological behavior of tumors and can thus aid in cancer diagnosis, treatment, and prognosis[31]. MiRNAs also participate in key signaling pathways, including mTOR/P-gp, Wnt/b-catenin, JAK/STAT, KRAS, EGF, and ERK[32,33]. MiR-145-5p is shown to act as a tumor suppressor in various cancers, including breast, cervical, bladder, renal, and gastrointestinal[34]. In non-small cell lung cancer, low expression of miR-145-5p is associated with pemetrexed resistance and EMT[35]. MiR-145-5p suppresses the early stage of colorectal cancer (CRC) but promotes metastasis at a later stage, indicating that it may play a dual role in this disease[36]. In esophageal squamous cell carcinoma, miR-145-5p attenuates proliferation, migration, and invasion[23], and in prostate cancer, miR-145-5p inhibits tumor growth and neuroendocrine differentiation[37]. These findings suggest that the role of miR-145-5p differs by cancer type. The current study demonstrated that miR-145-5p is downregulated in GC. The upregulation of this miRNA was shown to inhibit GC progression by preventing tumor cell migration, proliferation, invasion, and EMT and by promoting apoptosis. These findings are consistent with earlier studies showing that miR-145-5p targets ARF6, ANGPT2, N-cadherin, and ZEB2 and suppresses tumor cell malignancy in GC[38,39]. However, while SERPINE1 was identified as a target for...
miR-145-5p in oral squamous cell carcinoma (OSCC)\cite{27} the current study was the first to show that miR-145-5p also targets this gene in GC.

SERPINE1, or plasminogen activator inhibitor-1 (PAI-1), is an essential inhibitor of tissue plasminogen activator and urokinase-type\cite{40}. In CRC, overexpression of SERPINE1 is associated with tumor cell proliferation, invasion, and aggressiveness\cite{41}. SERPINE1 expression also correlates with the poor prognosis of head and neck squamous cell carcinoma, esophageal cancer, gastric adenocarcinoma, pancreatic ductal adenocarcinoma, and bladder cancer patients\cite{33,42,43}. The current study confirmed that SERPINE1 fosters GC cell proliferation, invasion, and migration while suppressing apoptosis, thereby reducing patient survival times. However, SERPINE1 expression varies across different tumor tissue types. The protein is dramatically overexpressed in colon, esophageal, GC, breast, and thyroid cancer tissues as well as in clear cell renal cells and head and neck squamous cell carcinomas. Meanwhile, SERPINE1 is notably downregulated in renal papillary cell carcinoma, hepatocellular carcinoma, renal chromophobe cell carcinoma, and endometrial cancer tissue\cite{44}. Several previous studies indicate that SERPINE1 is associated with angiogenesis and tumor progression in GC\cite{45-47}. MAFG-AS1 enhances bladder cancer tumorigenesis by regulating the miR-143-3p/SERPINE1 axis\cite{48}, and secretory SERPINE1 expression is increased by a purinergic P2Y12 inhibitor, inducing MMP1 expression and increasing colon cancer metastasis\cite{19}. A study on OSCC found that miR-617-targeted SERPINE1 inhibited OSCC cell proliferation, viability, and apoptosis\cite{50}. Notch1 regulates the aggressive phenotypes of differentiated thyroid cancer, which could also be mediated by SERPINE1 inhibition\cite{51}. Furthermore, SERPINE1 was shown to be upregulated in GC, showing a high diagnostic value, and associated with poorer overall survival and recurrence-free survival\cite{32,53}. SERPINE1 is also a member of the SERM signature and was identified as having great value in predicting GC treatment sensitivity, informing the development of targeted CSC and EMT-related therapies\cite{54}. These studies suggest that SERPINE1 may have functional specificity in different cell types due to the temporal and spatial expression of different upstream regulatory factors. The complex regulatory role of SERPINE1 in vivo and its close association with tumors suggest that identifying the regulatory mechanism of this protein will aid our understanding of GC pathogenesis. The current study confirmed that SERPINE1 expression was higher in several GC cell lines and tissues than in adjacent normal tissues. Further functional experiments demonstrated that SERPINE1 promotes GC cell proliferation, invasion, and metastasis while suppressing apoptosis. SERPINE1 overexpression could partially reverse the anti-tumor effect of miR145-5p mimics and promote EMT. In summary, SERPINE1 is targeted and regulated by miR-145-5p, promotes GC progression, and is associated with poor GC prognosis. These findings inform the development of novel therapeutic approaches or diagnostic tools for this disease.

**ERK1/2** is an important subfamily of mitogen-activated protein kinases that control various cellular activities and physiological processes, including promoting cell survival and pro-apoptotic functions under certain conditions\cite{55}. PAI-1 promotes the migration and invasion of ESCC cells and macrophages by activating the Akt and ERK1/2 signaling pathways\cite{56}. The current study indicated that SERPINE1 promoted the phosphorylation of ERK1/2 and expression of EMT-related mesenchymal markers (α-SMA, β-catenin, and vimentin), and inhibited the expression of epidermal marker E-cadherin, thus inducing GC cell proliferation, invasion, and migration. Furthermore, GC tumor growth in nude mice was inhibited after the addition of the PD98059 inhibitor, suggesting that SERPINE1 could promote the growth of GC. SERPINE1 expression was also detected in the tumors, confirming that it promotes tumor growth and EMT by stimulating ERK1/2 phosphorylation, inducing GC invasion and migration. Overexpression of miR-145-5p in SGC7901 cells reduced ERK1/2 phosphorylation, while SERPINE1 partially reversed its effect.

**Figure 5** Serpin family E member 1 is a potential target gene of microRNA-145-5p and is highly expressed in gastric cancer tissues and cells. A: A Venn diagram of overlapping mRNAs from the differentially expressed mRNAs in The Cancer Genome Atlas (TCGA)-STAD data and miRNA-145-5p (miR-145-5p) target genes predicted from the two bioinformatics databases; B: Box chart showing the differential expression of serpin family E member 1 (SERPINE1) in the normal and tumor data in TCGA-STAD; C: Overall survival curves of patients in the high (red) and low (blue) SERPINE1 expression groups; D: Differential expression of SERPINE1 mRNA (left panel) and protein (middle panel) in gastric cancer (GC) tissue and SERPINE1 mRNA (right panel) in the HGC27 and SGC7901 GC cell lines; scale bar = 20 μm; E: SERPINE1 mRNA and protein expression in the miR-145-5p mimic group in SGC7901 cells and the inhibitor group in HGC27 cells. \( P < 0.01; P < 0.001; P < 0.0001 \).
Figure 6 Effects of serpin family E member 1 overexpression on gastric cancer cell proliferation, invasion, migration, and apoptosis.  

A: Serpin family E member 1 (SERPINE1) mRNA and protein expression in lentivirus transfected SGC7901 cells;  
B: SERPINE1 overexpression promotes SGC7901 cell proliferation;  
C: SERPINE1 overexpression promotes SGC7901 cell colony formation;  
D: SERPINE1 promotes SGC7901 cell invasion; scale bar = 100 μm;  
E: SERPINE1 promotes SGC7901 cell migration; scale bar = 100 μm;  
F: SERPINE1 overexpression reduces SGC7901 cell apoptosis.  
*p < 0.05;  
**p < 0.01;  
***p < 0.001.
Figure 7 Serpin family E member 1 reverses microRNA-145-5p-mediated gastric cancer cell proliferation, invasion, metastasis, epithelial-mesenchymal transition, and apoptosis. A: Serpin family E member 1 protein expression in co-transfected cells; B: Co-transfected cell proliferation; C: Co-transfected cell colony formation; D: Co-transfected cell migration; scale bar = 100 μm; E: Co-transfected cell invasion; scale bar = 100 μm; F: Epithelial-mesenchymal transition-related marker protein (E-cadherin, β-catenin, Vimentin, and α-smooth muscle actin) expression in co-transfected cells; G: Apoptosis of co-transfected cells. *P < 0.05; †P < 0.01; ‡P < 0.001.

The current study has some important limitations. The relationship between miR-145-5p and different histological types and TNM stages of GC, the impact of Helicobacter pylori infection, and chemotherapeutic resistance were not assessed. The role of these factors will be assessed in follow-up studies to provide more theoretical support for the use of miR-145-5p in a clinical setting.

CONCLUSION

In conclusion, this is the first study to show that miR-145-5p inhibits GC cell proliferation, invasion, metastasis, and EMT, and promotes apoptosis by regulating the SERPINE1/ERK1/2 axis. The findings suggest that targeting this axis may serve as a potential GC treatment approach.
Figure 8 Effect of serpin family E member 1 overexpression on gastric cancer cell proliferation and the signal-regulated kinase-1/2 pathway in vitro and in vivo. A: Expression of signal-regulated kinase-1/2 (ERK1/2) and p-ERK1/2 in SGC7901 co-transfected cells; B: Image of xenograft tumors at day 18 post-inoculation; C: Xenograft tumor growth, volume, and mass at day-18 post-inoculation. n = 5 mice per group; D: Ki67 expression in xenograft tumor tissue; Scale bar = 20 μm; E: E-cadherin, vimentin, serpin family E member 1, ERK1/2, and p-ERK1/2 expression in xenograft tumor tissues. *P < 0.05; **P < 0.01; ***P < 0.001. SERPINE1: Serpin family E member 1; ERK1/2: Signal-regulated kinase-1/2.

ARTICLE HIGHLIGHTS

Research background
Gastric cancer (GC), a common malignancy of the digestive system, has an increasing incidence rate and poses a substantial threat to human health.

Research motivation
MicroRNAs (miRNA) play important roles in gene regulation and modulate many physical and pathological processes. The research motivation of this study was to identify the role of miRNA-145-5p (miR-145-5p) in the development of GC and its underlying mechanisms.

Research objectives
This study sought to compare miR-145-5p expression in GC and adjacent normal tissues, clarify the role of miR-145-5p in GC cell proliferation, invasion, metastasis, epithelial-mesenchymal transition (EMT), and apoptosis, and identify the direct target of miR-145-5p in GC cells.

Research methods
Real-time polymerase chain reaction was performed to detect miRNA expression. Wound-healing and Transwell assays were performed to evaluate cancer cell migration and invasion, respectively. Cell proliferation was examined using cell counting kit-8 and colony formation assays. Cell apoptosis was assessed using flow cytometry. Western blotting analysis was used to identify EMT-associated proteins. A dual-luciferase reporter system was used to validate the target of miR-145-5p. Tumor formation in nude mice was assessed to further explore the mechanism by which miR-145-5p inhibits the progression of GC.

Research results
MiR-145-5p was decreased in GC tissues. Serpin family E member 1 (SERPINE1) was characterized as a direct target of miR-363-3p. MiR-145-5p was shown to target SERPINE1 to regulate extracellular signal-regulated kinase-1/2 (ERK1/2) signaling.

Research conclusions
MiR-145-5p inhibits GC progression via the SERPINE1-ERK1/2 axis.

Research perspectives
The miR-145-5p/SERPINE1/ERK1/2 axis may serve as a GC treatment target.

FOOTNOTES

Author contributions: Bai HX and Qiu XM prepared material, data collection, analysis, and performed were design; Xu CH collected the samples; Bai HX and Xu CH performed animal experiments; Bai HX and Guo JQ wrote the manuscript. All authors read and approved the final manuscript. All authors contributed to the study’s conception and design.
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