Lenvatinib acts on platelet-derived growth factor receptor β to suppress the malignant behaviors of gastric cancer cells

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Abstract. Given the limited treatment options and high mortality rates associated with gastric cancer, there is a need to explore novel therapeutic options. The present study aimed to investigate the efficacy of lenvatinib, a multi-target tyrosine kinase inhibitor, in mitigating the progress of gastric cancer *in vitro*. Comprehensive analyses were conducted to assess the impact of lenvatinib on gastric cancer cells, focusing on the inhibition of viability, suppression of proliferation, induction of apoptosis and reduction of metastatic potential. The effects of lenvatinib on these activities were determined using 5-ethynyl-2'-deoxyuridine staining, colony formation assay, flow cytometry, western blotting, scratch assay and Transwell assay. In addition, bioinformatics analyses were employed to identify key regulatory targets of lenvatinib, with particular attention given to platelet-derived growth factor receptor β (PDGFRB). In addition, the effects of PDGFRB overexpression on the regulation of lenvatinib were explored. Lenvatinib demonstrated significant inhibitory effects on the viability, proliferation and metastatic capabilities of MKN45 and HGC27 gastric cancer cell lines. Bioinformatics analyses identified PDGFRB as a crucial target of lenvatinib, with its downregulation showing promise in enhancing overall survival rates of patients with gastric cancer. By contrast, PDGFRB overexpression reversed the effects of lenvatinib on cells. The present findings underscore the potential of lenvatinib as a promising therapeutic option in the treatment of gastric cancer. By elucidating its mechanism of action and identifying PDGFRB as a primary target, the present study may aid further clinical advancements.

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Introduction

Gastrointestinal cancer is a common cause of cancer-related mortality, of which gastric cancer exhibits the highest mortality rate of all the gastrointestinal cancers, largely due to the elusive nature of its early symptoms that lead to delays in treatment (1). Risk factors for gastric cancer include *Helicobacter pylori* infection, advancing age, excessive salt consumption and dietary imbalances (2). In early-stage gastric cancer, tumor infiltration typically remains confined to the mucosal or submucosal layers, irrespective of lesion size or lymph node metastasis (3,4). Timely detection and close monitoring of tumor progression are required to alleviate the disease burden and mitigate the mortality rates associated with gastric cancer (5). Presently, the increasing use of semi-invasive endoscopic and radiological techniques is expanding the number of treatable cases (6), and emerging studies aimed at discerning differentially expressed molecules are gaining traction in research (7,8). Initial attempts at employing dual therapy with first-line platinum drugs and the chemotherapeutic agent fluoropyrimidine yielded suboptimal outcomes in terms of patient survival, with median survival rates still being <1 year (2). By contrast, subsequent targeted therapeutic modalities approved for gastric cancer treatment, including trastuzumab, ramucizumab (an anti-angiogenic agent) and PD-1 monoclonal antibody, have shown promise (9). However, the prognosis for the disease remains poor, with the 5-year overall survival rate being ~25% across all stages and reducing to <5% for the late metastatic form of this type of cancer (10). Consequently, there is a need for enhanced therapeutic interventions for gastric cancer.

Lenvatinib, a multi-target tyrosine kinase inhibitor, exerts its inhibitory effects on vascular endothelial growth factor receptor 1-3, fibroblast growth factor receptor 1-4, platelet-derived growth factor receptors α and β (PDGFRB), and RET (11-13). Extensive research has indicated that lenvatinib possesses tumor-suppressive mechanisms (14). For example, it has been discovered to inhibit the proliferation of liver cancer cells both *in vivo* and *in vitro*, to curb the

proliferation, invasion and migration of gallbladder cancer cells, and to promote apoptosis via AKT signaling (15). Furthermore, lenvatinib has demonstrated efficacy in inducing apoptosis and autophagy in human papillary thyroid cancer cells (16). However, investigations (17,18) into the effects of lenvatinib on gastric cancer remain scarce. Notably, a preclinical study has indicated its potential to impede the growth of xenografts sourced from patients with gastric cancer (17). In addition, a finding from a phase II clinical trial in Japan suggested favorable outcomes when lenvatinib was combined with pembrolizumab, an immune checkpoint inhibitor, in the treatment of advanced gastric cancer (18). These observations indicate a plausible role for lenvatinib in suppressing the malignant progression of gastric cancer cells.

The present study aimed to further investigate the effects of lenvatinib on gastric cancer cells, elucidating underlying mechanisms through a combination of bioinformatics analyses and experimental validation. The present study aimed to establish a theoretical basis for the clinical application of lenvatinib in gastric cancer treatment.

Materials and methods

Cell culture and treatment. Gastric adenocarcinoma MKN45 and gastric carcinoma HGC27 cells (Ningbo Mingzhou Biotechnology Co., Ltd.) were cultured in RPMI 1640 medium (Gibco; Thermo Fisher Scientific, Inc.) supplemented with 15% fetal bovine serum (Gibco; Thermo Fisher Scientific, Inc.) and 1% penicillin-streptomycin solution (Ningbo Mingzhou Biotechnology Co., Ltd.). The culture environment was maintained at 37˚C with 5% CO_2.

The cells were seeded into a 6-well plate at a density of $2x10^5$ cells/well and were transfected with 2 μg pcDNA3.1 PDGFRB overexpression vector or an empty vector (NovoPro Bioscience, Inc.) using RFect reagent (Baidai; Changzhou EMI Biotechnology Co., Ltd.) at 37˚C. After transfection for 48 h at 37˚C, the cells were treated with lenvatinib (40 μM; Selleck Chemicals) for 24 h at 37˚C.

Cell Counting Kit-8 (CCK-8) assay. MKN45 and HGC27 cells were seeded into 96-well plates at a density of $3x10^3$ cells/well, and were incubated in the presence of gradient concentrations of lenvatinib (0-100 μM) for 24 h at 37˚C. Subsequently, 10 μl CCK-8 reagent was added to the wells. The optical density was measured at a wavelength of 450 nm using a microplate reader (Tecan Group, Ltd.) after 1 h of incubation. The percentage cell inhibition rate (%) was calculated using the following formula: Cell inhibition=(OD value of control group-OD value of experimental group)/(OD value of control group-OD value of blank group) x100.

5-Ethynyl-2'-deoxyuridine (EdU) staining. MKN45 and HGC27 cells were seeded into 96-well plates, and cell proliferation was assessed using the EdU staining kit (Beyotime Institute of Biotechnology). As aforementioned, MKN45 and HGC27 cells were treated with lenvatinib, transfected with Ov-PDGFRB or Ov-NC, and were then incubated with 10 μM EdU reagent for 2 h at 37˚C. The cells were washed twice with phosphate-buffered saline (PBS), fixed with 4% paraformaldehyde for 15 min at room temperature and the nuclei were stained with DAPI. Images of the stained cells were captured under a fluorescence microscope (Olympus Corporation).

Colony formation assay. MKN45 and HGC27 cells treated with lenvatinib and transfected with Ov-PDGFRB or Ov-NC were inoculated into culture dishes (500 cells/dish) and evenly dispersed. After culturing the cells for 14 days, they were fixed with 4% paraformaldehyde for 30 min at room temperature and stained with 0.1% crystal violet (Selleck Chemicals) for 30 min at room temperature. Images of visible colonies (≥50 cells) were captured under a light microscope and colonies were counted using ImageJ software (version 1.8; National Institutes of Health).

Flow cytometry. Cell apoptosis was analyzed using an Annexin V-FITC Apoptosis Detection kit (BD Biosciences). After being treated with lenvatinib and transfected with Ov-PDGFRB or Ov-NC, the MKN45 and HGC27 cells were digested with 0.25% trypsin and washed twice with PBS. The cells were then suspended in binding buffer, and were incubated with 5 μl Annexin V-FITC for 30 min, followed by incubation with 5 μl propidium iodide for 5 min at room temperature in the dark. Apoptosis was analyzed using a FACSCalibur flow cytometer (BD Biosciences) and FlowJo software (version 10.7.2; FlowJo LLC).

Western blotting. After MKN45 and HGC27 cells were treated with lenvatinib and transfected with Ov-PDGFRB or Ov-NC, total proteins were extracted using RIPA lysis buffer (Beyotime Institute of Biotechnology) and were quantified using a Nanodrop spectrophotometer (Thermo Fisher Scientific, Inc.). Protein samples (30 μg) were separated by SDS-PAGE (10% gel; Bio-Rad Laboratories, Inc.). PVDF membranes carrying transferred proteins were then blocked with 5% skimmed milk for 1 h at room temperature, followed by an overnight incubation with primary antibodies against Bax (cat. no. 50599-2-Ig; 1:8,000 dilution; Wuhan Sanying Biotechnology), Bcl-2 (cat. no. 12789-1-AP; 1:9,000 dilution; Wuhan Sanying Biotechnology), PDGFRB (cat. no. 3169S; 1,000 dilution; Cell Signaling Technology, Inc.) and GAPDH (cat. no. 10494-1-AP; 1:20,000 dilution; Wuhan Sanying Biotechnology) at 4˚C. Thereafter, the membranes were incubated with an HRP-conjugated goat anti-rabbit antibody (cat. no. SA00001-2; 1:5,000 dilution; Wuhan Sanying Biotechnology) at 37˚C for 1 h. Signals were visualized using an ECL Western Blotting substrate kit (BioVision, Inc.) and were analyzed using ImageJ software (version 1.8; National Institutes of Health).

Molecular docking analysis. The structure of Lenvatinib was drawn in the ChemDraw software (version 18.0) and then imported into OpenBabel software (version 2.3.1) for hydrogenation, and converted into a mol2 format file. Subsequently, the structure of PDGFRB (PDB ID: AF-P09619-F1) was obtained from the RCSB PDB (https://www.rcsb.org/). Thereafter, the protein PDGFRB file was opened in PyMOL software (version 2.2.0) to remove the excess water molecules, delete any irrelevant small ligands originally carried and to keep only the protein structure. As the downloaded protein structure had ligands, the original ligands were deleted and

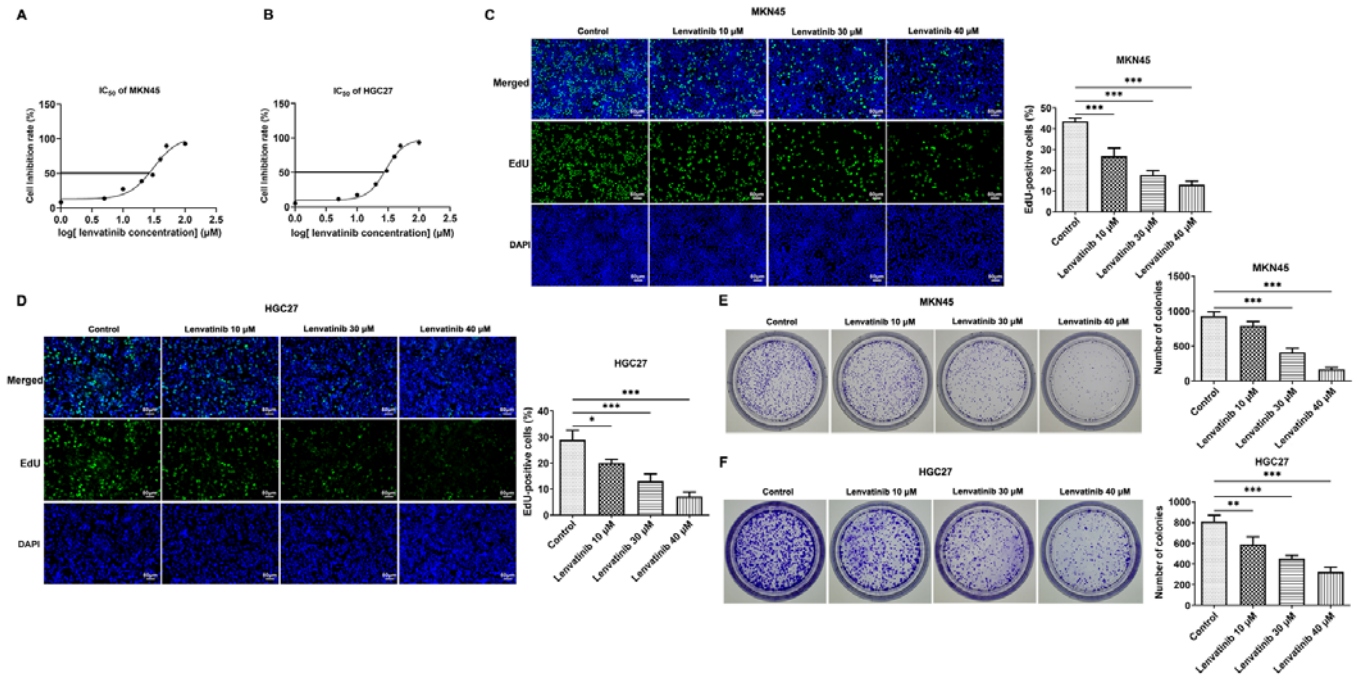

Figure 1. Effects of lenvatinib on gastric cancer cell proliferation and colony formation. Gradient concentrations of lenvatinib were applied to treat (A) MKN45 and (B) HGC27 cells, and their viability was measured at 24 h. Effects of lenvatinib on (C) MKN45 and (D) HGC27 cell proliferation were determined by EdU staining; scale bar, 50 μm. Effects of lenvatinib on colony formation of (E) MKN45 and (F) HGC27 cells were assessed. *P<0.05, **P<0.01, ***P<0.001. EdU, 5-ethynyl-2'-deoxyuridine.

the original ligand positions were set as the docking sites. AutoDock (version 1.5.6) (14) was used to display the specific docking energy value after running. Finally, the results were analyzed with the adoption of Protein-Ligand Interaction Profiler (PLIP; https://plip-tool.biotec.tu-dresden.de/plip-web).

Scratch assay. After being treated with lenvatinib and transfected with Ov-PDGFRB or Ov-NC, serum-starved MKN45 and HGC27 cells were grown until cells reached 90% confluence, and the central cells on the monolayer were scraped away using a 200-μl pipette tip. The distance of migration within 24 h was analyzed using ImageJ software (version 1.8) to calculate the migration rate under a light microscope.

Transwell assay. After being treated with lenvatinib and transfected with Ov-PDGFRB or Ov-NC, $1x10^5$ MKN45 or HGC27 cells suspended in fresh serum-free RPMI 1640 medium were seeded into the upper chamber of Transwell plates (8-μm pore size; Costar; Corning, Inc.) precoated with Matrigel at 37˚C for 30 min, and RPMI 1640 medium containing 20% FBS was added to the lower chamber. After a 24-h incubation at 37˚C, cells that passed through the Matrigel were stained with 0.5% crystal violet at room temperature for 10 min and were captured under a light microscope. The results were analyzed using ImageJ software (version 1.8).

Bioinformatics analysis. Differentially expressed genes between gastric cancer tissue and paired normal tissue obtained from the GSE79973 (19) and GSE118916 (20) datasets from the GEO database (ncbi.nlm.nih.gov/gds) were determined using the Limma package in R software (version 4.1.2; https://www.bioconductor.org/packages/release/bioc/html/limma.html). The differentially expressed genes in gastric cancer were acquired from The Cancer Genome Atlas (https://www.cancer.gov/ccg/research/genome-sequencing/tcga). The target genes of lenvatinib were analyzed through TargetNet (http://targetnet.scbdd.com/) and SuperPred (https://prediction.charite.de/) databases. A Venn diagram was generated to display intersection genes, and the Gene Expression Profiling Interactive Analysis (GEPIA) database (http://gepia.cancer-pku.cn/) was used to display the association between intersection genes and overall survival.

Statistical analysis. Statistical analysis was performed using GraphPad Prism software (version 9.5; Dotmatics) and quantitative data are presented as the mean ± SD of three independent experiments. One-way ANOVA and Tukey's post hoc test were used to determine statistical differences between multiple groups. P<0.05 was considered to indicate a statistically significant difference.

Results

Effects of lenvatinib on gastric cancer cell proliferation and colony formation. Gradient concentrations of lenvatinib (0-100 μM) were used to treat MKN45 and HGC27 cells, and their cell viability was measured at 24 h. According to the results of the CCK-8 assay, lenvatinib inhibited the viability of both cells in a concentration-dependent manner (Fig. 1A and B). Given that the IC_{50} values of lenvatinib in MKN45 and HGC27 cells were 30.75 and 29.03 μM at the 24-h time point, concentrations of lenvatinib at 0, 10, 30 and 40 μM were selected for subsequent assays. The effects of lenvatinib on cell proliferation were determined by EdU staining. Proliferation

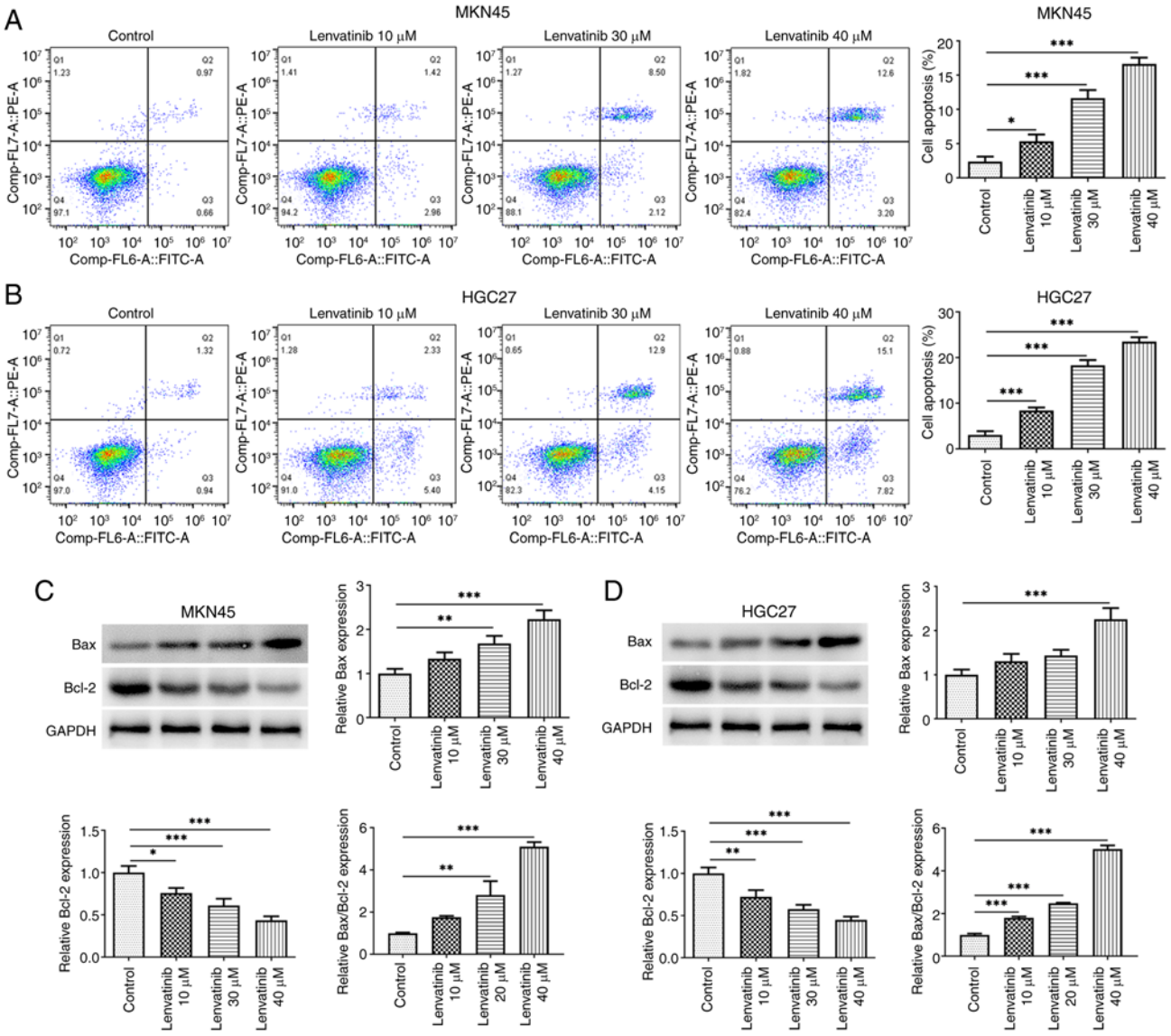

Figure 2. Effects of lenvatinib on gastric cancer cell apoptosis. Effects of lenvatinib on (A) MKN45 and (B) HGC27 cell apoptosis were evaluated by flow cytometry; comp-FL6-A and comp-FL7-A are the names of the channels. Western blot analysis revealed the effects of lenvatinib on the expression levels of apoptosis-related proteins in (C) MKN45 and (D) HGC27 cells. *P<0.05, **P<0.01, ***P<0.001.

levels were quantified by assessing the proportion of EdU-positive cells. It was discovered that Lenvatinib markedly suppressed the proliferation of MKN45 and HGC27 cells in a concentration-dependent manner (Fig. 1C and D). In addition, lenvatinib inhibited colony formation and the number of colonies visible to the naked eye was reduced (Fig. 1E and F).

Effects of lenvatinib on gastric cancer cell apoptosis and invasion. The effect of lenvatinib on MKN45 and HGC27 cell apoptosis was evaluated by flow cytometry. Lenvatinib increased the early and late apoptosis of both cells in a concentration-dependent manner (Fig. 2A and B). According to the results of western blot analysis, lenvatinib reduced Bcl-2 and increased Bax protein expression levels in cells, supporting the effect of lenvatinib on apoptosis (Fig. 2C and D). Scratch and Transwell assays were applied to evaluate the migration and invasion of the two cell lines, respectively. Lenvatinib significantly reduced the migration rate and the number of cells that invaded the matrix membrane, in both MKN45 (Fig. 3A and B) and HGC27 cells (Fig. 3C and D).

PDGFRB is a potential target of lenvatinib. Volcano plots displaying the differentially expressed genes in gastric cancer are shown in Fig. 4A and B. The Venn diagrams exhibit the intersection of the predicted targets of lenvatinib and the differentially upregulated (Fig. 4C) or downregulated (Fig. 4D) genes in gastric cancer, suggesting that only 8 upregulated genes in gastric cancer can act as potential targets of lenvatinib. As depicted in Fig. 4E, the hazard ratios of these eight intersection genes were exhibited in the heatmap, and PDGFRB, which had the highest hazard ratio in gastric cancer, was screened out. Based on GEPIA, low- and high-expression PDGFRB groups were classified based on the median expression of PDGFRB, and it was shown that high PDGFRB expression was associated with poor survival

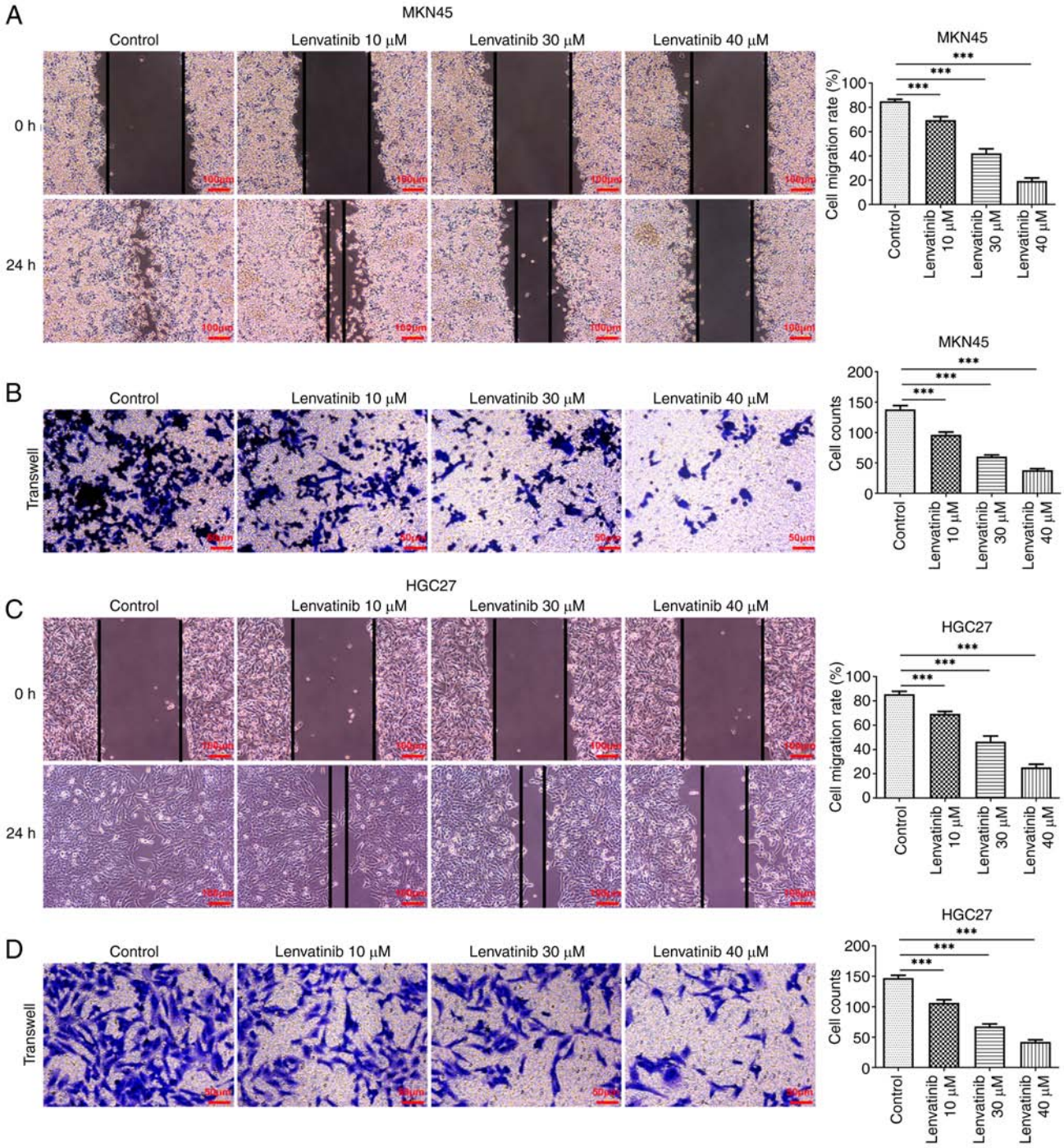

Figure 3. Effects of lenvatinib on gastric cancer cell invasion. (A) Scratch and (B) Transwell assays evaluated the migration and invasion of MKN45 cells. (C) Scratch and (D) Transwell assays evaluated the migration and invasion of HGC27 cells. Scale bar, 100 μm for scratch assay; scale bar, 50 μm for Transwell assay. ***P<0.001.

(Fig. 4F); therefore, the effect of lenvatinib on PDGFRB was subsequently studied. Molecular docking analysis revealed that lenvatinib formed multiple hydrogen bonds with PDGFRB (Fig. 4G), indicating that lenvatinib bound well to amino acids in the protein pocket. Western blot analysis indicated that the expression levels of PDGFRB in MKN45 and HGC27 cells were reduced in a concentration-dependent manner upon lenvatinib treatment (Fig. 4H). Furthermore, PDGFRB was successfully overexpressed by transfection of MKN45 and HGC27 cells with a pcDNA3.1 PDGFRB overexpression vector, which was confirmed by western blotting (Fig. 4I).

PDGFRB overexpression reverses the regulatory effects of lenvatinib. To explore the regulatory effects of lenvatinib on PDGFRB, cells were induced to overexpress PDGFRB, and the proliferation and colony formation of the cells were evaluated. The results demonstrated that PDGFRB overexpression promoted MKN45 and HGC27 cell proliferation (Fig. 5A and B) and colony formation (Fig. 5C and D), and reversed the inhibitory effects of lenvatinib. Flow cytometry (Fig. 6A and B) and apoptosis-related protein analysis (Fig. 6C and D) also revealed that PDGFRB overexpression reduced the proportion of apoptotic cells and the protein expression

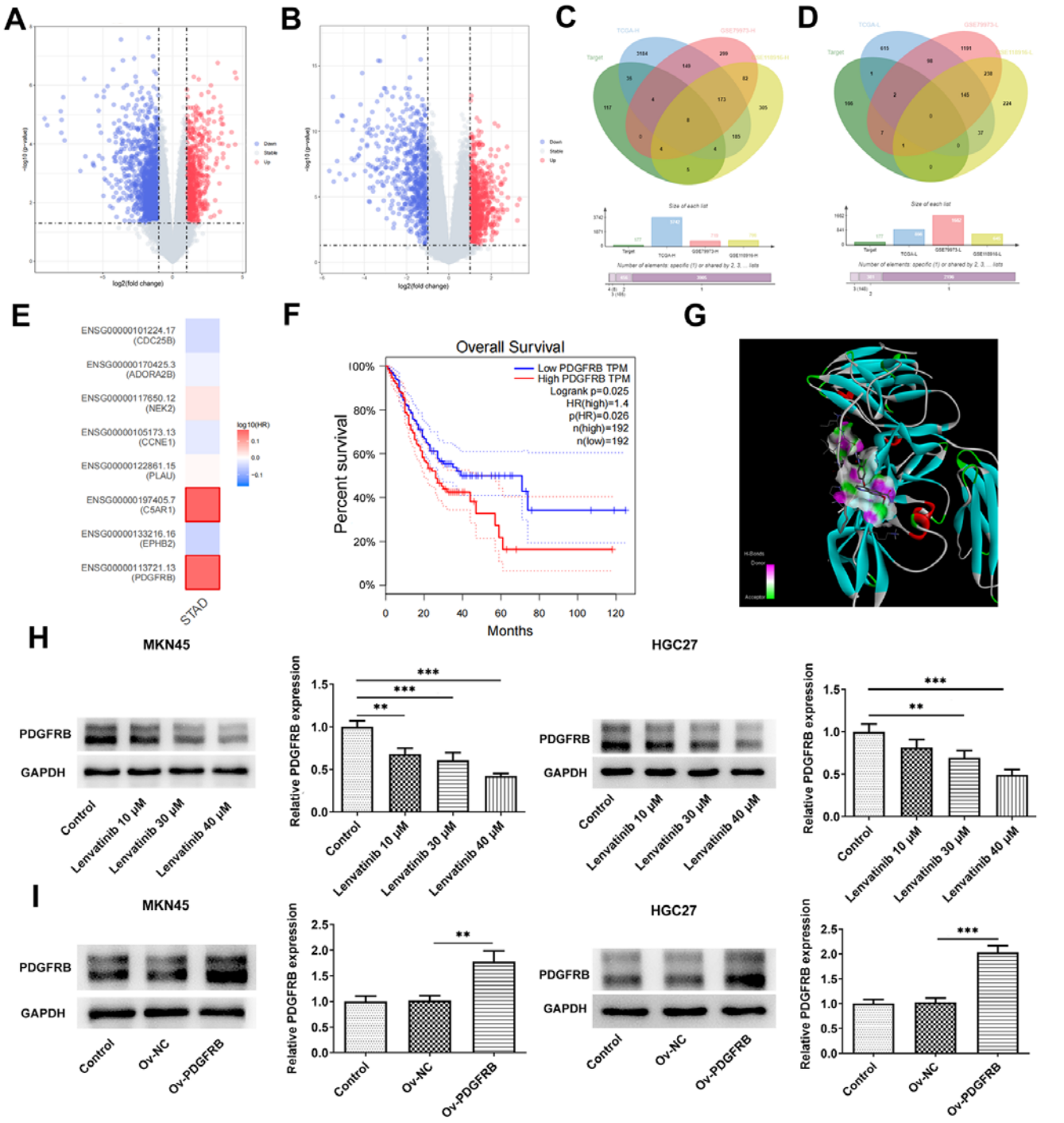

Figure 4. PDGFRB is a potential target of lenvatinib. Volcano plots of differentially expressed genes in gastric cancer, as determined using data from (A) GSE79973 and (B) GSE118916 datasets. Venn diagrams exhibiting the intersection of differentially expressed genes in gastric cancer and target genes of lenvatinib, as shown for (C) upregulated and (D) downregulated genes. (E) Correlation between eight intersection genes and patient overall survival rate was analyzed, with a deep color indicating a close correlation. (F) Gene Expression Profiling Interactive Analysis showed the association between PDGFRB levels and overall survival. (G) Molecular docking revealed that lenvatinib bound to amino acids in the PDGFRB protein. (H) Western blotting indicated the expression levels of PDGFRB upon lenvatinib treatment in MKN45 and HGC27 cells. (I) Western blotting indicated the overexpression levels of PDGFRB after transfection in MKN45 and HGC27 cells. **P<0.01, ***P<0.001. NC, negative control; Ov, overexpression vector; PDGFRB, platelet-derived growth factor receptor β; STAD, stomach adenocarcinoma.

levels of Bax, and increased the protein expression levels of Bcl-2 compared with the lenvatinib 40 μM + Ov-NC group. The migration and invasion of MKN45 (Fig. 7A and B) and HGC27 cells (Fig. 7C and D) were also enhanced in response to PDGFRB overexpression, compared with the negative control group, upon treatment with lenvatinib.

Discussion

The persistently high rates of mortality associated with gastric cancer underscore the ongoing limitations in treatment options. Patients with advanced gastric cancer often face challenges in pursuing radical surgical interventions (21),

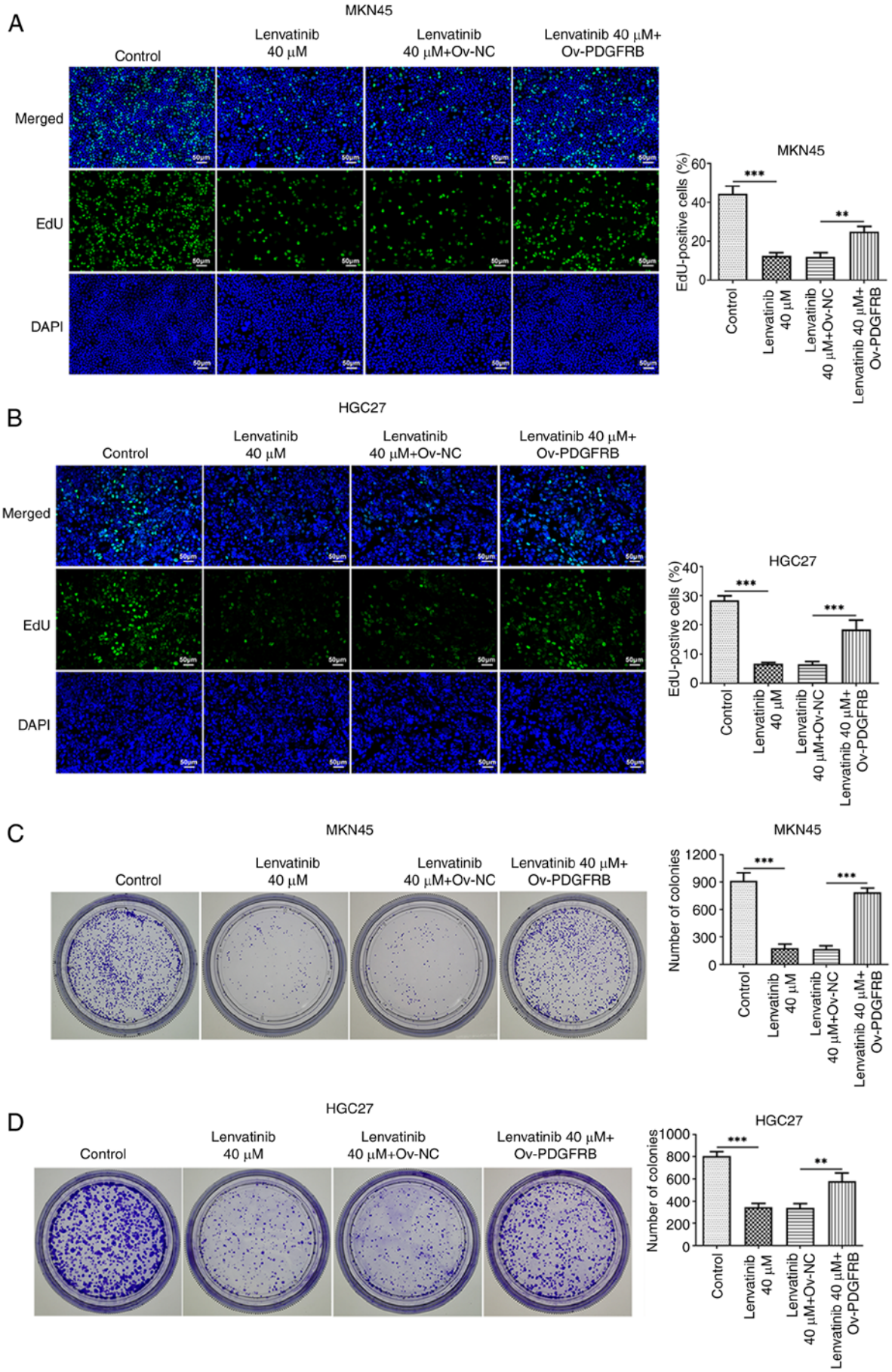

Figure 5. PDGFRB overexpression reverses the regulatory effects of lenvatinib on cell proliferation. Proliferation of (A) MKN45 and (B) HGC27 and colony formation of (C) MKN45 and (D) HGC27 cells were evaluated upon PDGFRB overexpression. Scale bar, 50 μm. **P<0.01, ***P<0.001. NC, negative control; Ov, overexpression vector; PDGFRB, platelet-derived growth factor receptor β.

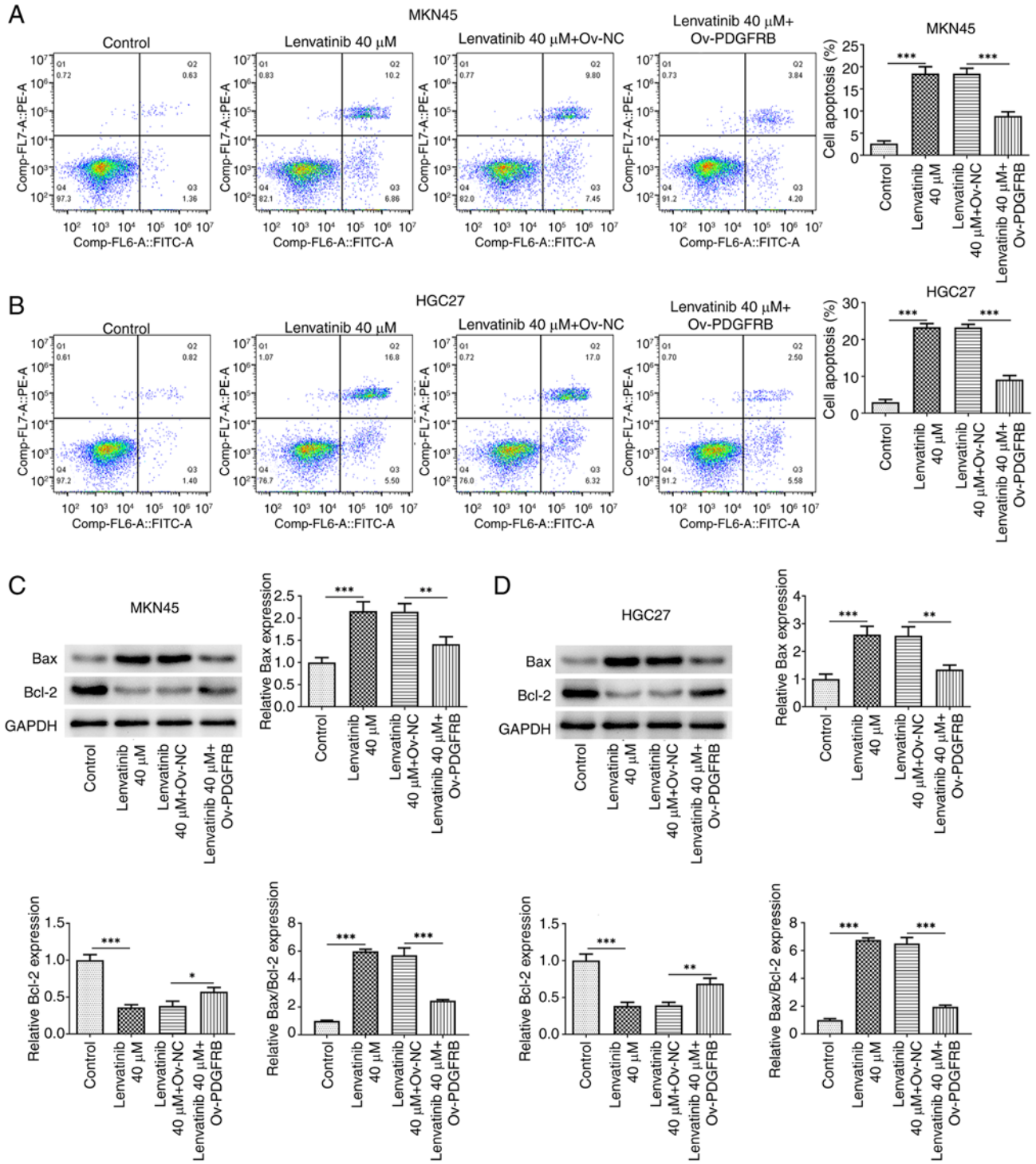

Figure 6. PDGFRB overexpression reverses the regulatory effects of lenvatinib on cell apoptosis. Effects of PDGFRB overexpression on (A) MKN45 and (B) HGC27 cell apoptosis were evaluated by flow cytometry; comp-FL6-A and comp-FL7-A are the names of the channels. Western blot analysis revealed the effect of PDGFRB overexpression on the expression levels of apoptosis-related proteins in (C) MKN45 and (D) HGC27 cells. *P<0.05, **P<0.01, ***P<0.001. NC, negative control; Ov, overexpression vector; PDGFRB, platelet-derived growth factor receptor β.

leaving combination chemotherapy as the predominant therapeutic option (22,23). Nonetheless, the existing array of chemotherapeutic agents remains limited in efficacy, while being markedly associated with toxicity and side effects (24). By contrast, molecular targeted therapies offer a promising alternative characterized by reduced toxicity and enhanced efficacy (25). Consequently, the aim to identify novel molecular targeted drugs has emerged as a focal point in contemporary gastric cancer research. The advent of small molecule tyrosine kinase inhibitors has heralded advancements in the management of various types of cancer, including gastric cancer (26). Within this area, the present study focused on lenvatinib, aiming to elucidate its potential in impeding the malignancy of gastric cancer cells. The experimental findings indicated the capacity of lenvatinib to inhibit the viability and proliferation of MKN45 and HGC27 cells while enhancing apoptosis.

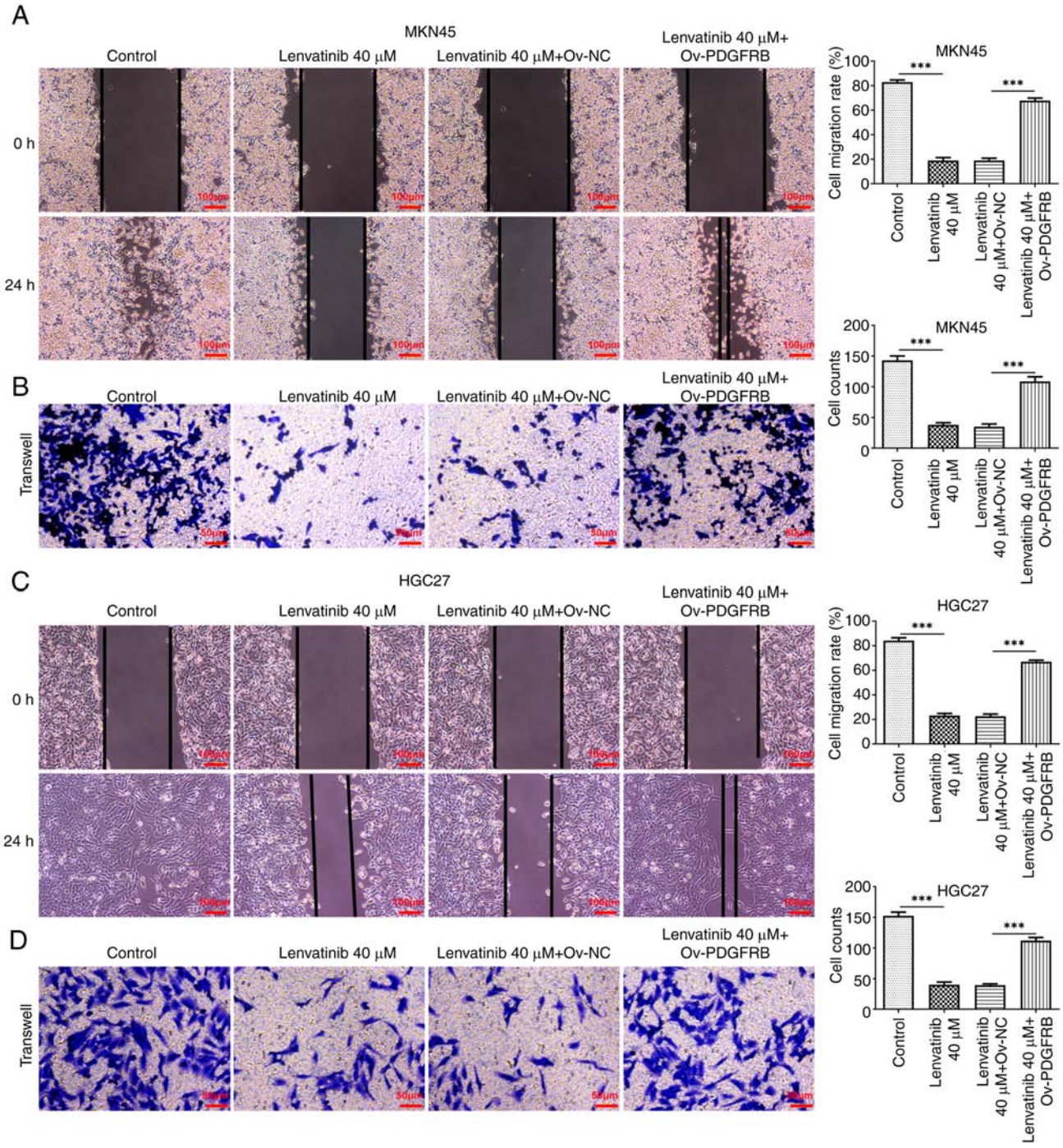

Figure 7. PDGFRB overexpression reverses the regulatory effects of lenvatinib on cell migration and invasion. (A) Scratch and (B) Transwell assays evaluated the effect of PDGFRB overexpression on the migration and invasion of MKN45 cells. (C) Scratch and (D) Transwell assays evaluated the effect of PDGFRB overexpression on the migration and invasion of HGC27 cells. ***P<0.001. Scale bar, 100 μm for scratch assay; scale bar, 50 μm for Transwell assay. NC, negative control; Ov, overexpression vector; PDGFRB, platelet-derived growth factor receptor β.

Furthermore, given the pivotal role of metastasis in dictating cancer outcomes, the impact of lenvatinib on the migratory capabilities of these cells was scrutinized. Notably, lenvatinib treatment exhibited a suppressive effect on the migration and invasion of both cell lines, underscoring its potential as a metastasis-inhibiting agent in gastric cancer.

Given the multi-target nature of lenvatinib (27), bioinformatics analyses were performed to determine its principal regulatory targets in gastric cancer. Through an intersectional analysis of lenvatinib-targeted genes and differentially expressed genes in gastric cancer tissues, eight genes of interest were identified. Subsequent analyses implicated PDGFRB as a prominent target, with data from the GEPIA database corroborating its inverse association with overall survival rates. Notably, prior research has underscored the pivotal role of PDGFRB in the metaplasia and dysplasia stages of gastric carcinogenesis (28). Moreover, synergistic interactions between PDGFRB blockade and anti-PD-1 immunotherapy have shown promise in impeding tumor growth, underscoring the interplay between stromal reprogramming and immune

modulation in gastric cancer management (29). Another study has shown that PDGFRB is closely related to immune cell infiltration in gastric cancer, especially M2 macrophage infiltration (30). These studies all indicate the beneficial effects of inhibiting PDGFRB levels on disease management, supporting the potential use of lenvatinib for the treatment of gastric cancer. Although this study explored the potential mechanism of lenvatinib in the context of gastric cancer using two cell lines, it still has certain limitations, such as the lack of *in vivo* experimental data, which will be a part of future studies.

In conclusion, the present study identified the ability of lenvatinib to inhibit the malignant phenotype of MKN45 and HGC27 cells, with PDGFRB emerging as a pivotal mediator of its actions. Coupled with the findings of bioinformatics analyses, these results highlight PDGFRB as a primary target of lenvatinib in gastric cancer management. With more clinical research being performed on lenvatinib, it may have a future role in cancer therapeutics.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

XT, JD and SC contributed to design, and performed experiments and manuscript drafting. QJ, QW and SZ contributed to methods and data analysis. XT and SC confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Machlowska J, Baj J, Sitarz M, Maciejewski R and Sitarz R: Gastric cancer: Epidemiology, risk factors, classification, genomic characteristics and treatment strategies. Int J Mol Sci 21: 4012, 2020.
2. Smyth EC, Nilsson M, Grabsch HI, van Grieken NC and Lordick F: Gastric cancer. Lancet 396: 635-648, 2020.
3. Yang K, Lu L, Liu H, Wang X, Gao Y, Yang L, Li Y, Su M, Jin M and Khan S: A comprehensive update on early gastric cancer: Defining terms, etiology, and alarming risk factors. Expert Rev Gastroenterol Hepatol 15: 255-273, 2021.
4. Conti CB, Agnesi S, Scaravaglio M, Masseria P, Dinelli ME, Oldani M and Uggeri F: Early gastric cancer: Update on prevention, diagnosis and treatment. Int J Environ Res Public Health 20: 2149, 2023.
5. Xia JY and Aadam AA: Advances in screening and detection of gastric cancer. J Surg Oncol 125: 1104-1109, 2022.
6. Repetto O, Vettori R, Steffan A, Cannizzaro R and De Re V: Circulating proteins as diagnostic markers in gastric cancer. Int J Mol Sci 24: 16931, 2023.
7. Farran B, Müller S and Montenegro RC: Gastric cancer management: Kinases as a target therapy. Clin Exp Pharmacol Physiol 44: 613-622, 2017.
8. Röcken C: Predictive biomarkers in gastric cancer. J Cancer Res Clin Oncol 149: 467-481, 2023.
9. Ajani JA, D'Amico TA, Bentrem DJ, Chao J, Cooke D, Corvera C, Das P, Enzinger PC, Enzler T, Fanta P, *et al*: Gastric cancer, version 2.2022, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 20: 167-192, 2022.
10. Zeng Y and Jin RU: Molecular pathogenesis, targeted therapies, and future perspectives for gastric cancer. Semin Cancer Biol 86: 566-582, 2022.
11. Li AY, McCusker MG, Russo A, Scilla KA, Gittens A, Arensmeyer K, Mehra R, Adamo V and Rolfo C: RET fusions in solid tumors. Cancer Treat Rev 81: 101911, 2019.
12. Albarrán V, Villamayor ML, Chamorro J, Rosero DI, Pozas J, San Román M, Calvo JC, Pérez de Aguado P, Moreno J, Guerrero P, *et al*: Receptor tyrosine kinase inhibitors for the treatment of recurrent and unresectable bone sarcomas. Int J Mol Sci 23: 13784, 2022.
13. Fleuren EDG, Vlenterie M and van der Graaf WTA: Recent advances on anti-angiogenic multi-receptor tyrosine kinase inhibitors in osteosarcoma and ewing sarcoma. Front Oncol 13: 1013359, 2023.
14. Chakraborty E and Sarkar D: Emerging therapies for hepatocellular carcinoma (HCC). Cancers (Basel) 14: 2798, 2022.
15. Liu YC, Hsu FT, Chung JG, Weng MC, Ting CY, Tsai CJ, Lan A, Wu JY, Lin CC and Lin SS: Lenvatinib induces AKT/NF-κB inactivation, apoptosis signal transduction and growth inhibition of non-small cell lung cancer in vivo. Anticancer Res 41: 2867-2874, 2021.
16. Fallahi P, Ferrari SM, Galdiero MR, Varricchi G, Elia G, Ragusa F, Paparo SR, Benvenga S and Antonelli A: Molecular targets of tyrosine kinase inhibitors in thyroid cancer. Semin Cancer Biol 79: 180-196, 2022.
17. Kawazoe A, Fukuoka S, Nakamura Y, Kuboki Y, Wakabayashi M, Nomura S, Mikamoto Y, Shima H, Fujishiro N, Higuchi T, *et al*: Lenvatinib plus pembrolizumab in patients with advanced gastric cancer in the first-line or second-line setting (EPOC1706): An open-label, single-arm, phase 2 trial. Lancet Oncol 21: 1057-1065, 2020.
18. Fei HJ, Chen SC, Zhang JY, Li SY, Zhang LL, Chen YY, Chang CX and Xu CM: Identification of significant biomarkers and pathways associated with gastric carcinogenesis by whole genome-wide expression profiling analysis. Int J Oncol 52: 955-966, 2018.
19. Liu H, Qu Y, Zhou H, Zheng Z, Zhao J and Zhang J: Bioinformatic analysis of potential hub genes in gastric adenocarcinoma. Sci Prog 104: 368504211004260, 2021.
20. Karalis JD, Yoon LY, Hammer STG, Hong C, Zhu M, Nassour I, Ju MR, Xiao S, Castro-Dubon EC, Agrawal D, *et al*: Lenvatinib inhibits the growth of gastric cancer patient-derived xenografts generated from a heterogeneous population. J Transl Med 20: 116, 2022.
21. Sexton RE, Al Hallak MN, Diab M and Azmi AS: Gastric cancer: A comprehensive review of current and future treatment strategies. Cancer Metastasis Rev 39: 1179-1203, 2020.
22. Li K, Zhang A, Li X, Zhang H and Zhao L: Advances in clinical immunotherapy for gastric cancer. Biochim Biophys Acta Rev Cancer 1876: 188615, 2021.
23. Guan WL, He Y and Xu RH: Gastric cancer treatment: Recent progress and future perspectives. J Hematol Oncol 16: 57, 2023.
24. Yang WJ, Zhao HP, Yu Y, Wang JH, Guo L, Liu JY, Pu J and Lv J: Updates on global epidemiology, risk and prognostic factors of gastric cancer. World J Gastroenterol 29: 2452-2468, 2023.
25. Patel TH and Cecchini M: Targeted therapies in advanced gastric cancer. Curr Treat Options Oncol 21: 70, 2020.

26. Blay JY, Kang YK, Nishida T and von Mehren M: Gastrointestinal stromal tumours. Nat Rev Dis Primers 7: 22, 2021.
27. Zhao Y, Zhang YN, Wang KT and Chen L: Lenvatinib for hepatocellular carcinoma: From preclinical mechanisms to anti-cancer therapy. Biochim Biophys Acta Rev Cancer 1874: 188391, 2020.
28. Lee SH, Contreras Panta EW, Gibbs D, Won Y, Min J, Zhang C, Roland JT, Hong SH, Sohn Y, Krystofiak E, *et al*: Apposition of fibroblasts with metaplastic gastric cells promotes dysplastic transition. Gastroenterology 165: 374-390, 2023.
29. Akiyama T, Yasuda T, Uchihara T, Yasuda-Yoshihara N, Tan BJY, Yonemura A, Semba T, Yamasaki J, Komohara Y, Ohnishi K, *et al*: Stromal reprogramming through dual PDGFRα/β blockade boosts the efficacy of anti-PD-1 immunotherapy in fibrotic tumors. Cancer Res 83: 753-770, 2023.
30. Liu B, Xiao X, Lin Z, Lou Y and Zhao L: PDGFRB is a potential prognostic biomarker and correlated with immune infiltrates in gastric cancer. Cancer Biomark 34: 251-264, 2022.

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