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ZNF655 mediated by LINC01210/miR-124-3p axis promotes the progression of gastric cancer

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Abstract

Gastric cancer (GC) is a common malignant tumor that usually originates from the epithelium of the gastric mucosa. ZNF655 was a suppressor gene of many cancers. However, the mechanism of ZNF655 in GC remains unknown. Quantitative polymerase chain reaction was used to assess the expression of ZNF655, LINC01210, and miR-124-3p. Western blotting was used to monitor ZNF655 protein expression. MTT, clone formation, transwell, and flow cytometry were all used to investigate the functions of GC cells. The interactions between ZNF655, LINC01210, and miR-124-3p were confirmed using the dual-luciferase reporter gene assay and the RIP assay. ZNF655 was highly expressed in GC cells. ZNF655 knockdown reduced GC cell viability, proliferation, migration, invasion, and induced apoptosis. The level of miR-124-3p was significantly reduced in GC cells. Besides, miR-124-3p targeted ZNF655 and inhibited its expression. MiR-124-3p mimics inhibited GC cell progression, but ZNF655 overexpression reversed these effects. Moreover, LINC01210 was found to be highly expressed in GC cells and to be able to sponge miR-124-3p. Furthermore, inhibiting miR-124-3p or increasing ZNF655 could counteract the effects of LINC01210 knockdown on GC cell development. Finally, ZNF655 promoted GC cell progression and was regulated by the LINC01210/miR-124-3p axis.

KEYWORDS
GC, LINC01210, miR-124-3p, ZNF655

1 | INTRODUCTION

Gastric cancer (GC) is a common type of digestive system malignant tumor.[1] The incidence and mortality rates of GC are ranked fifth and fourth worldwide, respectively.[2] Surgery is still the most effective method in the early and late stages of GC.[3] Advanced GC may also require a combination of chemotherapy and radiation therapy, but the 5-year overall survival is still <30%.[4] Therefore, more research is required to detect the occurrence of GC at an early stage or to improve the prognosis.

Long noncoding RNAs (lncRNAs) are noncoding RNAs with lengths >200 nts that play important roles in cancer.[5,6] Increasing evidence suggests that lncRNAs are abnormally expressed in cancer and can regulate biological functions such as proliferation and apoptosis. For instance, LINC00470 acted as an oncogenic gene, promoting GC cell growth by mediating the stability of PTEN mRNA.[7] Furthermore, LINC00511 was found to be abnormally high in colorectal cancer, which facilitated colorectal cancer progression by adjusting miR-124-3p and mediating EZH2.[8] In ovarian cancer, LINC01210 epigenetically decreased KLF4 expression and accelerated proliferation, invasion, and migration of the cancer cells.[9] However, the biological functions of LINC001210 in GC remain unknown.

MicroRNAs (miRNAs) are noncoding RNAs extensively involved in post-transcriptional gene silencing and play important roles in disease occurrence and development.[10,11] As previously reported, miR-199a-3p accelerated GC progression by targeting ZHX1.[12] MiR-506-3p inhibited colorectal cancer proliferation by decreasing EZH2 expression.[13] Additionally, growing evidence suggests that lncRNAs, acting as endogenous decoys for miRNAs, sponge miRNAs to modulate their target genes, involved in the progression of many diseases.[14] In oral squamous cell carcinoma, lncRNA SNHG20 mediated cell growth by adjusting the miRNA-19b-3p/RAB14 axis.[15] MiR-124-3p was found to be less expressed in GC and functioned as a tumor suppressor, and its overexpression inhibited GC development.[16] Bioinformatic analysis suggested that LINC01210 and miR-124-3p bond with each other. Nonetheless, it has not been reported whether the LINC01210/miR-124-3p axis plays a role in GC development, which warrants further investigation.

Zinc finger protein 655 (ZNF655) is a member of the Krüppel-like zinc finger gene family with a typical zinc finger structure. It is essential in modulating the biological functions of cells. A growing body of evidence suggests that zinc finger proteins are closely related to cancer progression.[17] Such as, ZHX1 was reported to be able to induce cell-cycle arrest and apoptosis to prevent GC development.[18] ZNF545 acted as a tumor suppressor, inhibiting colorectal cancer progression via multiple signal pathways.[19] ZNF281 has been identified as an oncogenic gene in pancreatic cancer by promoting cell growth and invasion.[20] Moreover, the Krüppel-like zinc finger gene could be used to regulate cancer's biological function as a miRNA target. As previously demonstrated, miR-491-5p could bind to ZNF-703 and inhibit breast cancer migration and invasion.[21] Although ZNF655 has been studied for its role in the progression of non-small cell lung cancer, there is still uncertainty in GC. Concurrently, we discovered that ZNF655 could be a target of miR-124-3p. Therefore, we hypothesized that miR-124-3p might regulate GC progression by mediating ZNF655 expression.

Here, we investigated the functions of ZNF655 in GC and its latent molecular mechanisms. The results showed that LINC01210/miR-124-3p axis modulated ZNF655 and accelerated the viability, proliferation, migration, and invasion of GC cells while inhibiting GC cells apoptosis. Therefore, our findings revealed that ZNF655 might become a novel treatment for GC.

2 | METHODS

2.1 | Cell culture

GES-1, AGS, and MKN45 cells were obtained from Bank of the (Shanghai, China). All cells were cultured in Dulbecco's Modified Eagle's Medium (Thermo Fisher Scientific, Waltham, MA), to which 10% fetal bovine serum (FBS; Gibco, Carlsbad, California), 1% penicillin and streptomycin (Sigma-Aldrich, Merck, Germany) were added. All cells were cultivated under the 37°C and 5% CO_2 conditions.

2.2 | RNA isolation, reverse transcription, and real-time quantitative polymerase chain reaction

The total RNA was obtained from GC cells. TRIzol reagent (Invitrogen, Carlsbad, California) was used to isloated the total RNA. cDNA was synthesized with PrimeScript RT reagent Kit (Takara, Tokyo, Japan), and SYBR Premix Ex Taq II kit (Takara) was used for quantitative polymerase chain reaction (qPCR). qPCR referred to the following protocol: 2 min at 94°C, followed by 35 cycles (94°C for 30 s and 55°C for 45 s). All data were calculated by using the $2^{-\Delta\Delta ct}$ formula. GAPDH or U6 was used as control. The primer sequences were as follows:

LINC01210 (F): 5′-AGCCCTCAACGGAAATCCTG-3′.
LINC01210 (R): 5′-GGGCTGTTTCTCTCAAGGGT-3′.
miR-124-3p (F): 5′-GCCGAGTAAGGCACGCGGTGAA-3′.
miR-124-3p (R):
5′-GTGCAGGGTCCGAGGT-3′.
ZNF655 (F): 5′-GGAGGAAATACCAGCCCAGG-3′.
ZNF655 (R): 5′-GCACTTGCCTGGGTATGACT-3′.
GAPDH (F): 5′-TCAAGAAGGTGGTGAAGCAGG-3′.
GAPDH (R): 5′-TCAAAGGTGGAGGAGTGGGT-3′.
U6 (F): 5′-CGCTTCGGCAGCACATATAC-3′.
U6 (R): 5′-AAATATGGAACGCTTCACGA-3′.

2.3 | Western blotting

The total protein was obtained from GC cells treated with RIPA lysis buffer (Beyotime, Shanghai, China). The total protein concentration was detected using BCA Assay Kit (Beyotime, Shanghai, China). Proteins (40 μg per lane) were isolated using sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) (10%). SDS-PAGE separated proteins were then transferred to PVDF membranes. Then, the membranes were blocked for 1 h with 5% skimmed milk. Subsequently, primary antibodies ZNF655 (1:1000, 25–557; ProSci, California) and GAPDH (1:1000, 437,000; Thermo, Waltham, Massachusetts) were used as controls to incubate the PVDF membranes overnight at 4°C, and HRP-conjugated secondary antibodies (1:2000, ab6728; Abcam, Cambridge, UK) were used to incubate the membranes for 1 h. ECL kit (Thermo, Waltham, Massachusetts) was used to visualize the protein bands. The densitometry analysis was measured using IPP 6.0 (Image-Pro Plus 6.0).

2.4 | Cell transfection

The overexpression plasmid of ZNF655 (OE-ZNF655), the short hairpin RNA of ZNF655 (sh-ZNF655), LINC01210 (sh-LINC01210), and miR-124-3p mimics/inhibitor, as well as their negative control groups (pcDNA3.1, sh-NC, mimics NC, and inhibitor NC), were purchased from GenePharma (Shanghai, China). For in vitro transfection, AGS and MKN45 cells were transfected with OE-ZNF655, sh-ZNF655, sh-LINC01210, miR-124-3p inhibitor, or miR-124-3p mimics and their corresponding negative control groups using Lipofectamine™ 3000 (Invitrogen, California) according to the manufacturer's instructions.

2.5 | MTT assay

Cells were seeded into 96-well plates (1×10^3 cells/well) overnight and cultured for 24, 48, or 72 h. The cells were then treated for 4 h with an MTT solution (20 μl). A microplate reader (Thermo, Waltham) was used to measure the absorbance of each well at 490 nm.

2.6 | Clone formation assay

GC cells were seeded on 6-well plates (1×10^3 cells/well) in each group and incubated at 37°C. Two weeks later, cells were fixed with methanol on ice environment, after being stained with 0.1% crystalized violet (Sigma-Aldrich, Merck, Germany), and the number of cloned cells was determined. The experiment required at least three-time repetitions.

2.7 | Transwell assay

Cell migration and invasion of GC cells were processed with trypsin and resuspended in the serum-free medium. GC cells (4.0×10^4 cells/well) were transferred into the upper chamber (Corning, Inc., New York, New York) for the migration assay. The Matrigel invasion chamber (1.0×10^5 cells/well; Corning, Inc.) was used for the invasion assay. The lower chambers contained 600 μl of medium supplemented with 10% FBS. Cells were incubated at 37°C for 24 h. Then, 4% paraformaldehyde and 0.1% crystal violet solution were used to fix and stain cells that migrated or invaded to the lower chambers. Cells that remained in the upper chamber were carefully removed with cotton swabs. The cells were then imaged with a digital camera under a microscope (Leica DMI1, Shanghai, China) from five random fields of view.

2.8 | Flow cytometry assay

On the basis of the corresponding manual, cells were collected after various treatments, washed in PBS, and resuspended in 500 μl of 1 × Annexin-binding buffer. The cells were then cultured in the dark at room temperature with 10 μl Annexin V-FITC and 5 μl PI stain from the Annexin V-FITC apoptosis detection kit (Beyotime, Shanghai, China). Samples were immediately detected using flow cytometry after a 10 min incubation period. Annexin V staining was detected as green fluorescence and PI as red fluorescence.

2.9 | Dual-luciferase reporter assay

The LINC01210 or ZNF655 sequences that bind with miR-124-3p were cloned into pGL6 vectors (Beyotime, Shanghai, China) for constructing reporter vectors LINC01210 (WT/MUT) or ZNF655 (WT/MUT). Lipofectamine 3000 was used to transfect miR-124-3p mimics or inhibitors into GC cells coupled with LINC01210 (WT/MUT) or ZNF655 (WT/MUT). A Dual-Luciferase Reporter Assay System (Promega, WI) was used to measure luciferase activity.

2.10 | RNA-binding protein immunoprecipitation

The association of miR-124-3p with ZNF655 and miR-124-3p with LINC01210 were examined using a RIP assay kit (Sigma-Aldrich, Merck, Germany). In summary, the anti-Ago2 antibody immunoprecipitated the miRNA, and immunoglobulin G (IgG) served as the negative control. ZNF655, miR-124-3p, and LINC01210 enrichment were evaluated using qPCR.

2.11 | Statistical analysis

Each experimental group repeated three times, yielding three independent data points. All data were presented as mean ± SD. Additionally, GraphPad Prism 6 was used to analyze the data. The student's *t*-test was used to analyze the significant between two groups, and one-way analysis of variance was used to explain more than two groups. A statistically significant difference was defined as $p < 0.05$.

3 | RESULTS

3.1 | ZNF655 expression was largely elevated in GC cells, and ZNF655 reduction inhibited cell growth

To investigate the biological functions of ZNF655 in GC, the ZNF655 level in GC cells was first determined. ZNF655 mRNA and protein expression were abnormally high in GC cells compare to the GES-1 normal cells (Figure 1A,B). Subsequently, the shRNA targeting ZNF655 was used to reduce ZNF655 expression in both AGS and MKN45 cells. It was observed that sh-ZNF655 transfection significantly reduced ZNF655 expression in GC cells (Figure 1C,D). Then, the viability, proliferation, migration, and invasion of GC cells were significantly impaired, whereas the apoptosis was significantly increased after ZNF655 knockdown (Figure 1 E–I). Therefore, these results revealed that ZNF655 was increased in GC cells and ZNF655 suppression inhibited GC cell growth.

3.2 | miR-124-3p mediated GC cell viability, proliferation, migration, and apoptosis by targeting ZNF655

Primarily, miR-124-3p expression was significantly reduced in GC cells (Figure 2A). The binding sequences for miR-124-3p and ZNF655 were obtained from the Starbase website (Figure 2B). Additionally, miR-124-3p mimic/inhibitor repressed/raised luciferase

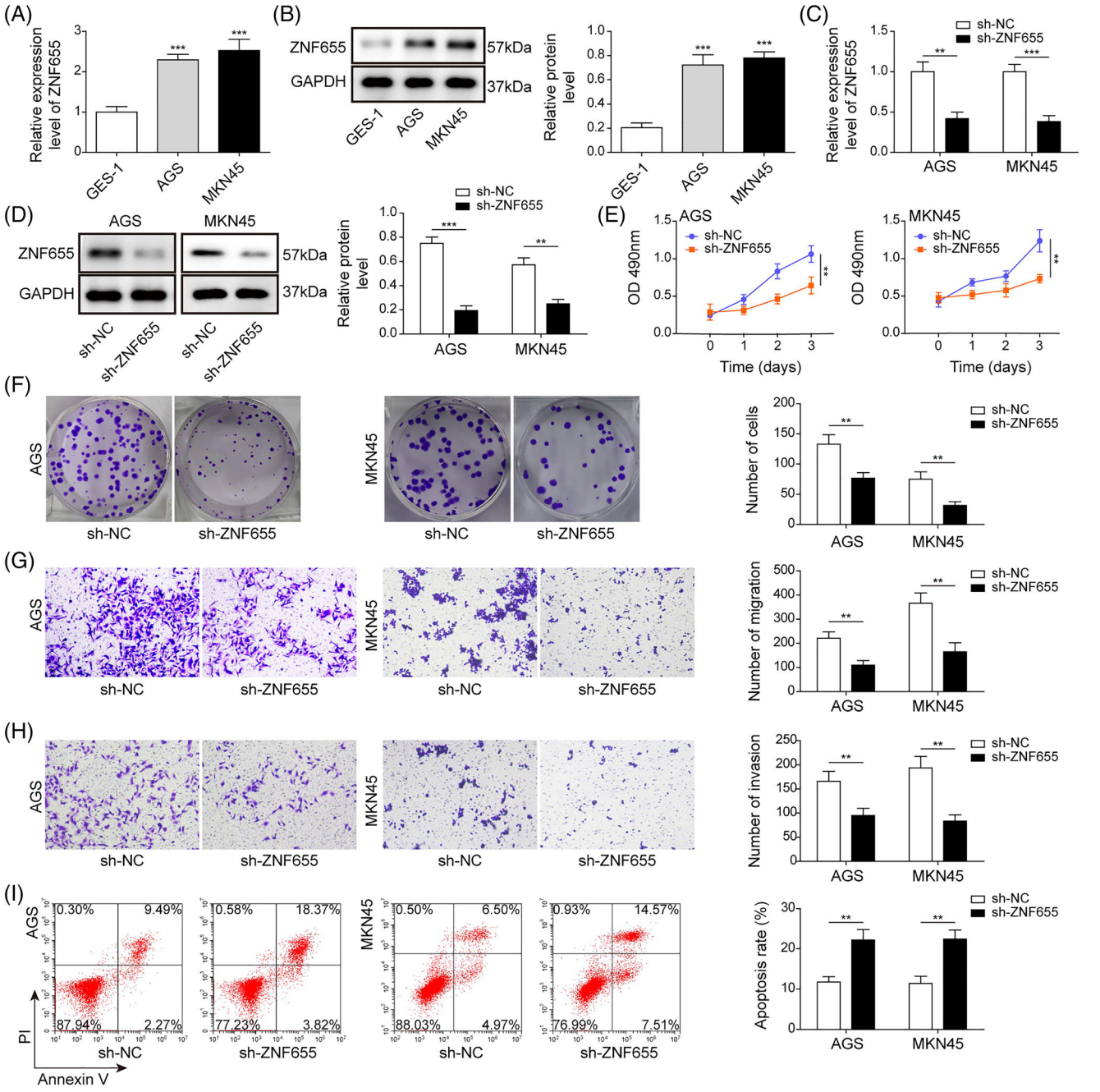

FIGURE 1 ZNF655 expression was largely elevated in gastric cancer (GC) cells, and ZNF655 reduction inhibited cell growth. (A) The mRNA level of ZNF655 in GES-1, AGS, and MKN45 cells was monitored by quantitative polymerase chain reaction (qPCR). (B) The protein expression of ZNF655 in GES-1, AGS, and MKN45 cells was examined using western blotting. AGS cells as well as MKN45 cells underwent sh-NC and sh-ZNF655 transfection. (C) The mRNA level of ZNF655 was detected using qPCR. (D) The protein level of ZNF655 was evaluated by western blotting. (E) MTT assay was employed to determine cell viability. (F) A clone formation assay was applied to examine cell proliferation. (G and H) Transwell assay was used to measure the migration and invasion in GC cells. (I) Flow cytometry assay was applied to evaluate cell apoptosis. $^{*}p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$.

activity in the ZNF655-WT group whereas the ZNF655-MUT group showed no change in luciferase activity (Figure 2C). The RIP assay revealed a relationship between ZNF655 and miR-124-3p (Figure 2D). Moreover, miR-124-3p mimic reduced ZNF655 expression, which was reversed by ZNF655 overexpression (Figure 2E). Meanwhile, miR-124-3p mimic hampered cell proliferation, migration, invasion, and accelerated cell apoptosis, but these effects were mitigated by increased ZNF655 (Figure 2F–J). miR-124-3p interacted with ZNF655 to regulate GC cell proliferation, migration, and apoptosis.

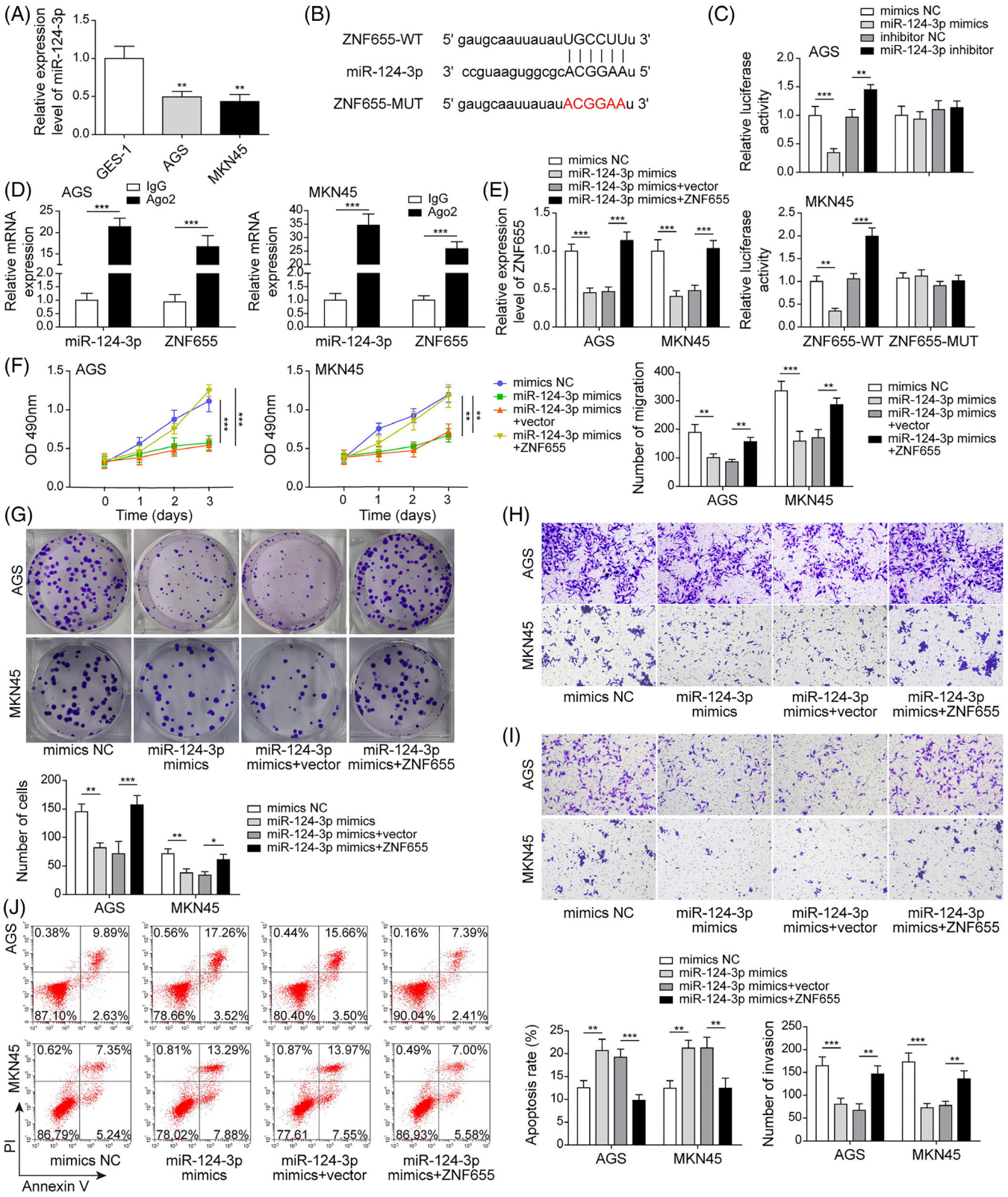

FIGURE 2 miR-124-3p mediated gastric cancer (GC) cell viability, proliferation, migration, and apoptosis via targeting ZNF655. (A) miR-124-3p expression in GES-1, AGS and MKN45 cells were assessed using quantitative polymerase chain reaction (qPCR). (B) The binding site between miR-124-3p and ZNF655. Its combination was confirmed by dual-luciferase reporter assay (C) and RIP (D). AGS and MKN45 cells suffered from mimics NC, miR-124-3p mimics, miR-124-3p mimics + vector, and miR-124-3p mimics + ZNF655 transfection. (E) The mRNA of ZNF655 was measured using qPCR. (F) MTT determined cell viability. (G) A clone formation assay was applied to examine cell proliferation. (H and I) Transwell assay was used to measure the migration and invasion of cells. (J) Cell apoptosis was evaluated by flow cytometry. $^{*}p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$.

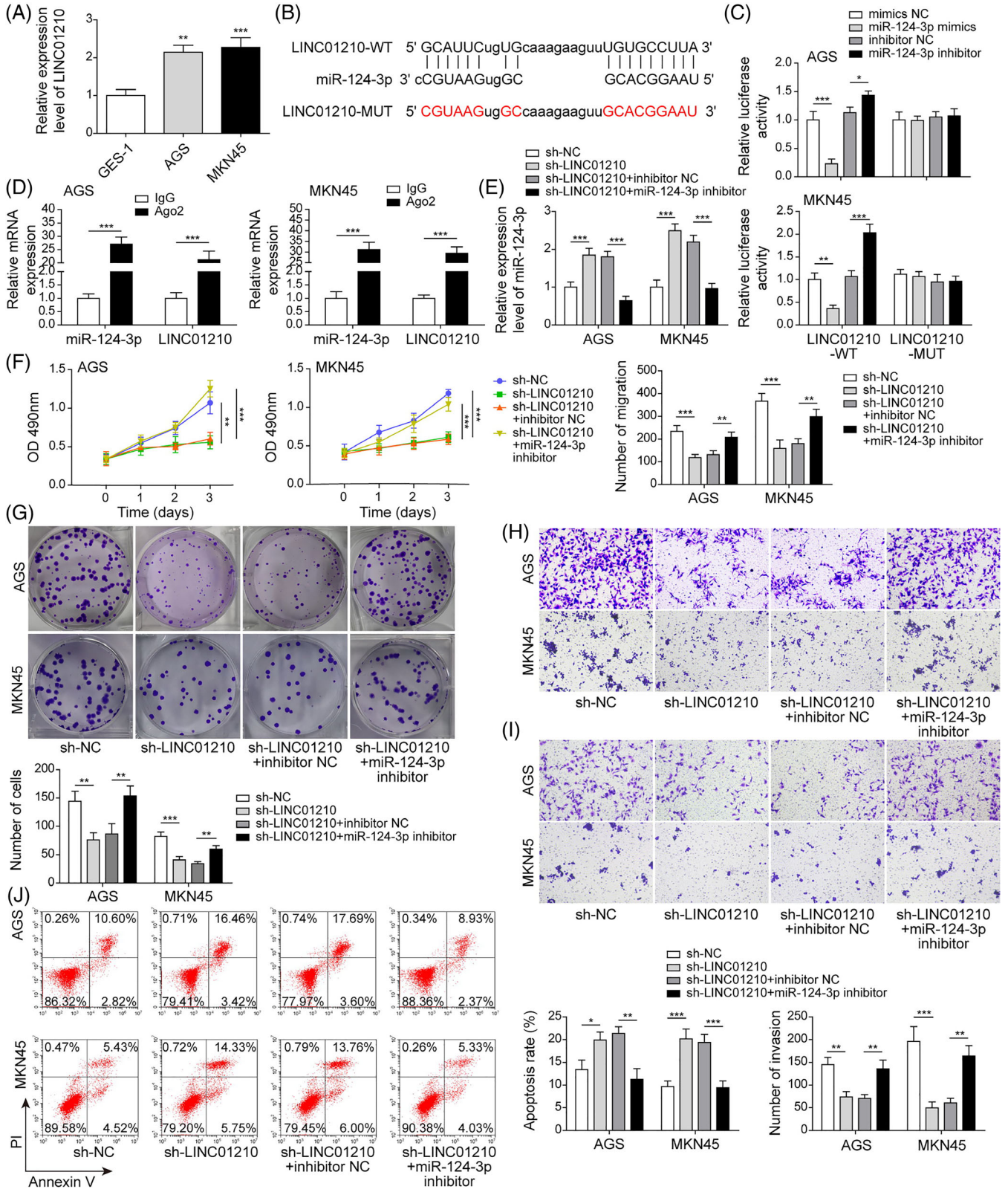

FIGURE 3 LINC01210 regulated gastric cancer (GC) cell viability, proliferation, migration, and apoptosis in combination with miR-124-3p. (A) LINC01210 expressions in GES-1. AGS and MKN45 cells were assessed using quantitative polymerase chain reaction (qPCR). (B) The binding site between miR-124-3p and LINC01210. The dual-luciferase reporter assay (C) and RIP (D) validated their interaction. AGS and MKN45 cells underwent transfection with sh-NC, sh-LINC01210, sh-LINC01210 + inhibitor NC, and sh-LINC01210 + miR-124-3p inhibitor. (E) qPCR was applied to measure miR-124-3p expression. (F) MTT assay was employed to determine cell viability. (G) A clone formation assay was applied to examine cell proliferation. (H and I) Transwell assay was used to measure the migration and invasion of cells. (J) Cell apoptosis was evaluated by flow cytometry. *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$.

3.3 | LINC01210 regulated GC cell viability, proliferation, migration, and apoptosis with miR-124-3p

To investigate the role of LINC01210 in the progression of GC cells, the level of LINC01210 was detected in AGS and MKN45 cells. LINC01210 expression was significantly increased in GC cells (Figure 3A). A putative binding site between LINC01210 and miR-124-3p was predicted by LncBase website analysis (Figure 3B). miR-124-3p mimics/inhibitors reduced/enhanced luciferase activity in WT-LINC01210 but did not affect luciferase activity in MUT-LINC01210 (Figure 3C). LINC01210 and miR-124-3p were enriched in Ago2 immunoprecipitants rather than IgG (Figure 3D). Subsequently, LINC01210 knockdown increased miR-124-3p expression, but transfection with a miR-124-3p inhibitor reduced the effect of LINC01210 knockdown on the expression of miR-124-3p in GC cells (Figure 3E). Additionally, LINC01210 deficiency reduced AGS and MKN45 cell viability, proliferation, migration, and invasion while

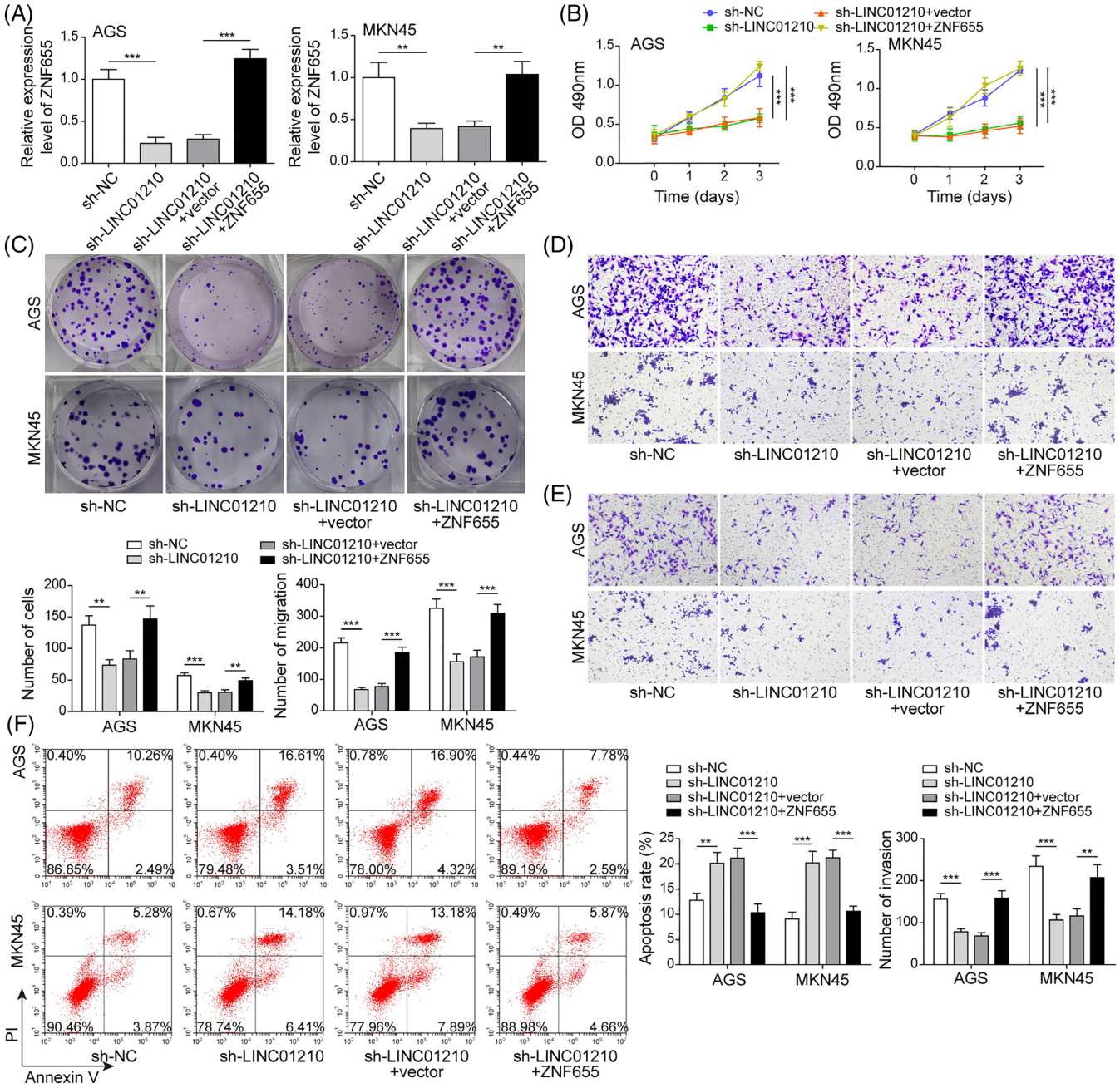

FIGURE 4 LINC01210 impeded the development of GC through the mediation of ZNF655. AGS and MKN45 cells underwent transfection with sh-NC, sh-LINC01210, sh-LINC01210 + vector, and sh-LINC01210 + OE-ZNF655. (A) ZNF655 level was tested using quantitative polymerase chain reaction. (B) MTT determined cell viability. (C) Cell proliferation was examined by clone formation. (D and E) Transwell assay was used to measure the migration and invasion of cells. (F) Cell apoptosis was evaluated by flow cytometry. *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$.

increasing apoptosis, which was reversed by miR-124-3p knockdown (Figure 3F–J). Thus, LINC01210 facilitated the progress of GC cells by inhibiting miR-124-3p.

3.4 | LINC01210 promoted the development of GC through mediation of ZNF655

AGS and MKN45 cells were transfected with sh-LINC01210 alone or in combination with overexpression of ZNF655 to determine the effects of ZNF655 on the LINC01210-mediated biological function of GC cells. Results from Figure 1A found that ZNF655 decreased in GC cells transfected with sh-LINC01210 alone, whereas ZNF655 overexpression reversed the effect of LINC01210 depletion on ZNF655 expression (Figure 4A). Furthermore, overexpression of ZNF655 was found to be effective in reversing the effects of LINC01210 knockdown on decreasing cell viability, proliferation, migration, invasion, and increasing apoptosis in AGS and MKN45 cells (Figure 4B–F). All these results indicated that LINC01210 could regulate ZNF655 expression and affect the function of GC cells.

4 | DISCUSSION

GC has a high incidence and mortality rate, with more than 1 million new cases and ~769,000 deaths in 2020.[2] As a result, GC causes enormous costs and suffering to people worldwide. The significance of zinc finger proteins in GC has received increasing attention in recent years. For example, ZNF479 increased the proliferation and glycolysis of GC cells.[22] Here, we observed that ZNF655 levels were significantly higher in GC cell lines. Functional experiments revealed that LINC01210/miR-124-3p regulated ZNF655, expression and involved in the progression of GC.

ZNF655, as a Krüppel-like zinc finger gene, has been reported in several types of cancer.[23–25] ZNF655 plays an important role in the progression of nonsmall cell lung cancer.[24] Moreover, ZNF655 was downregulated in glioma-associated endothelial cells, and ZNF655 overexpression inhibited glioma-associated endothelial cell angiogenesis.[25] These results suggested that ZNF655 plays opposite roles in various cancers. In this study, ZNF655 functioned as an oncogene in GC cells and was upregulated in GC cells. ZNF655 promoted the cell viability, proliferation, migration, invasion, and inhibited apoptosis in GC.

MiRNA has recently emerged as a hot research topic in multiple diseases, particularly in cancer.[26–28] MiRNA has been widely reported in the GC.[29,30] miR-491-5p was lowly expressed in GC and negatively regulated GC progression.[29] Here, miR-124-3p expression was significantly reduced in GC cells, and miR-124-3p negatively regulated the cell viability, proliferation, migration, and apoptosis in GC. These findings corroborated previous research.[31] Additionally, miRNAs are partially or entirely complementary to the 3′-UTR region of target genes, playing post-transcriptional regulatory roles. In this study, miR-124-3p interacted with ZNF655 and suppressed its expression, limiting GC cell growth.

LncRNAs were widely involved in numerous cancer processes and studies in GC.[32,33] For instance, the high LINC00511 expression is connected with accelerating GC progression.[32] LncRNA MYLK-AS1 was identified as an oncogene in GC, promoting proliferation, cell cycle, migration, and invasion in GC cells.[34] However, it is unclear whether LINC01210 is important in GC. As previously reported, LINC01210 epigenetically downregulated KLF4 and facilitated the development of ovarian cancer.[9] LINC01210 was abnormally highly expressed in GC cells and could promote proliferation, migration, invasion, and inhibit apoptosis in GC cells, similar to its effects on ovarian cancer. These findings suggested that LINC01210 had an oncogenic role in GC. A well-known classical regulatory mechanism of lncRNA–miRNA interaction is that lncRNAs compete for miRNAs to regulate miRNA target genes.[35,36] As previously reported, lncRNA PVT1 promotes cetuximab resistance of head and neck squamous cell carcinoma cells by inhibiting miR-124-3p.[37] Besides, LINC00240 knockdown increased miR-124-3p, which inhibited cell viability, proliferation, migration, and EMT in GC.[31] We found that LINC01210 could downregulate miR-124-3p expression and knockdown of LINC1210 suppressed the viability, proliferation, migration, invasion, and promote apoptosis of GC cells, which could be offset by miR-124-3p inhibitor. Simultaneously, LINC1210 could indirectly regulate ZNF655 levels, and ZNF655 could reverse the effects of LINC01210 silencing in GC cells.

In conclusion, our study first demonstrated ZNF655 endogenous expression and its effects on GC cell biological functions. Moreover, our findings revealed that ZNF655 was modulated by the LINC01210/miR-124-3p axis and facilitated the progression of GC, implying that ZNF655 could be a marker or therapeutic target for GC.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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