

LCN2 Mediated by IL-17 Affects the Proliferation, Migration, Invasion and Cell Cycle of Gastric Cancer Cells by Targeting SLPI

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Introduction: Gastric cancer occurred in China and even the whole East Asia with high incidence. The objective of this study was to investigate the role of *IL-17* in gastric cancer cells mediated by *LCN2* binding to *SLPI*.

Methods: The expression of *LCN2* and *SPLI* in gastric cancer cells and transfection effects were confirmed by RT-qPCR analysis. The proliferation, clone formation ability, invasion, migration, apoptosis, and cell cycle of gastric cancer cells were in turn detected by CCK-8 assay, clone formation assay, transwell assay, wound healing assay, and flow cytometry analysis. The combination between *LCN2* and *SLPI* was determined by co-immunoprecipitation assay. The expression of *Caspase-3*, *Bcl-2*, *cyclinB1*, *cyclinD1*, *MMP9*, and *SLPI* in gastric cancer cells was detected by Western blot analysis.

Results: *LCN2* and *SPLI* exhibited the highest levels in AGS cells, and thus AGS cells were selected for the next experiments. Down-regulation of *LCN2* suppressed the proliferation and clone formation ability of AGS cells treated with *IL-17*. *IL-17* promoted the invasion and migration of AGS cells, which was partially reversed by the down-regulation of *LCN2*. Down-regulation of *LCN2* mediated by *IL-17* promoted apoptosis and suppressed the cell cycle of AGS cells.

Discussion: Down-regulation of *LCN2* mediated by *IL-17* suppressed the proliferation and suppressed the migration and invasion and cell cycle of gastric cancer cells by targeting *SLPI*.

Keywords: lipocalin-2, LCN2, interleukin-17, IL-17, gastric cancer cells, SLPI

Introduction

Gastric cancer is one of the most common malignant gastrointestinal tumors. According to relevant statistics, the incidence of gastric cancer ranks fourth while its mortality rate ranks second among all malignant tumors. Meanwhile, China's statistics illustrated that both the incidence and the mortality of gastric cancer rank first among gastrointestinal malignant tumors.¹ Every year, about 700,000 patients in the world die from gastric cancer, and there are about 1 million newly developed gastric cancer cases.² China, as a country with a high incidence of gastric cancer, accounts for 25% of the new gastric cancer cases in the world. The prognosis of gastric cancer patients is very poor, with the 5-year survival rate <25%.³ Therefore, it is urgent to explore the molecular mechanism of the occurrence and development of gastric cancer for the further development of new therapeutic strategies for gastric cancer.

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Interleukin-17 (*IL-17*) is a cytokine mainly produced by Th17 cells with multiple biological effects. It can induce the production of a variety of cytokines, chemokines, inflammatory effector substances and antimicrobial proteins, and thus participate in a variety of autoimmune diseases and infectious inflammation.⁴ A number of clinical studies have shown that *IL-17* or *IL-17* mRNA levels can be detected in peripheral blood or tumor tissues of patients with gastric cancer, medulloblastoma, ovarian cancer, colorectal carcinoma, lung cancer, and breast cancer.^{5–9} *IL-17* can promote the carcinogenesis in breast cancer, lung cancer, colon cancer, and gastric cancer.¹ By KEGG (<https://www.genome.jp/kegg/pathway.html>), *LCN2* is found to be a downstream protein of the *IL-17/NF-κB* pathway, and it can be activated by *IL-17*.

Lipocalin-2 (*LCN2*) is a neutrophil gelatinase-associated lipocalin mainly secreted by hepatocytes.¹⁵ It has been found that *LCN2* plays a key role in the differentiation, proliferation, angiogenesis, invasion, and metastasis of tumor cells.^{16,17} Furthermore, it is abnormally expressed in cervical cancer, oral squamous cell carcinoma, colorectal cancer, and breast cancer.^{16–19} High expression of *LCN2* can promote the invasion and metastasis of tumor cells by enhancing *MMP9* activity^{17,20} and inducing epithelial-mesenchymal transformation (EMT).^{21,22} By STRING (<https://string-db.org>), *LCN2* can combine with secretory leukocyte peptidase inhibitor (*SLPI*), which is highly expressed in gastric cancer, and can promote the proliferation, invasion, and metastasis of gastric cancer cells.²³

Overall, we speculated that *IL-17* might affect the proliferation, migration and invasion, and cell cycle of AGS cells, and it could mediate *LCN2* which binds to *SLPI*.

Materials and Methods

Cell Culture and Cell Transfection

Gastric parietal cell line (HGT-1 cells) and gastric cell lines (N87, Fu97, AGS and MKN-45 cells) were provided from Shanghai Zishi Biotechnology Co., Ltd. (Shanghai, China). The cells were cultured in RPMI-1640 medium supplemented with 10% FBS, 10 μg/mL streptomycin, and 100 U/mL penicillin, and they were incubated at 37°C with 5% CO₂ in a humidified atmosphere. Routine liquid exchange and subculture were conducted. Gastric cancer cells at the logarithmic growth stage were re-suspended after digestion, counted, and planked. The plasmids of

shRNA-NC, shRNA-*LCN2*-1, and shRNA-*LCN2*-2 were transfected with the Lipofectamine[®]2000 Reagent at 70% ~80% cell density on the next day.

RT-qPCR Analysis

The total RNA from gastric cancer cells was extracted with Trizol reagent. According to the manufacturer's instructions, a reverse transcription kit was used to reverse transcribe the RNA into cDNA. AceQ qPCR SYBR Green Master Mix kit was used for the quantitative analysis of mRNA in qPCR. β-Actin was used as the internal reference.

CCK-8 Assay

Gastric cancer cells were treated with *IL-17*, and gastric cancer cells transfected with shRNA-NC or shRNA-*LCN2* were also treated with *IL-17*. All cells were planted in 96-well plates at the density of 5000 cells/mL and incubated in a 5% CO₂ and 37°C incubator for 24 h. 10 μL CCK-8 reagent was added to each well and the optical density at 450 nm was determined 2 h later.

Clone Formation Assay

After indicated treatment, all cells were planted in a culture dish containing 10 mL culture medium, cultured at 37°C, incubated for 14 days, and cloned successfully. The cells were fixed with 4% paraformaldehyde for 15 min, and the crystal violet staining solution was added for 20 min, followed by the microscopic observation.

Wound Healing Assay

After indicated treatment, cell suspension at the density of 5×10⁵ cells/mL was routinely cultured to monolayer cells. Sterile 100 μL yellow shot was used to draw a straight line on monolayer-cultured cells to form a cell-free growth area (scratch). The width of scratch area was recorded, and then the shed cells were washed with serum-free medium. After 24 h of conventional culture, the images were observed and obtained under an inverted microscope.

Transwell Assay

Matrigel was pre-coated in the transwell chamber. After indicated treatment, cells were re-suspended to a concentration of 1×10⁵ cells/mL in culture medium of 1% fetal bovine serum. And, 100 μL cell suspension was added to the upper chamber, and 900 μL culture medium containing 10% serum was added to the lower chamber. After 24 h, the transwell chamber was taken out, fixed with 4%

paraformaldehyde for 30 min and stained with crystal violet for 20 min. Finally, the images were observed and obtained under an optical microscope.

Flow Cytometry Analysis

Gastric cancer cells at the logarithmic phase were incubated in the six-well plates with each well containing 5×10^5 cells. After treatment of *IL-17*, cisplatin (DDP), and transfection, cells were cultured in an incubator for another 48 h. The cells were digested with EDTA-free pancreatic enzyme and collected into a centrifuge tube. The cells were centrifuged at 1000 r/min for 5 min and the supernatant was discarded. Then, cells were washed with cold PBS, centrifuged at 1000 r/min for 5 min to discard the supernatant and blended with binding buffer to be transferred to a flow tube. Five microlitres of Annexin V and propidium iodide (PI) were added to the cells, which were mixed gently and kept away from light at 4°C for 20 min. After staining, 0.5 mL binding buffer was added to each flow tube, and the apoptotic ratio and cell cycle of each tube were determined by flow cytometry.

Co-Immunoprecipitation Assay

The gastric cells at the logarithmic growth phase were added with cell lysis buffer and placed on the ice for lysis. After centrifugation at 4°C, the supernatant was taken and corresponding antibodies were added, respectively. After incubation at 4°C for 1 h, protein A/G agarose beads were added. Then, the protein A/G glycoprotein beads in the precipitation were gently washed and rinsed with cell lysis buffer for three times. Finally, the protein loading buffer was added and boiled in boiling water for 5 min. Western blot was used to detect the target proteins and confirm the binding proteins.

Western Blot Analysis

The logarithmic growth phase cells were collected, treated with *IL-17* and DDP, and transfected. The total cell protein was extracted with RIPA on ice. After full lysis, the cells were isolated at 10,000 r/min at 4°C for 10 min. The supernatant was taken and the protein concentration was determined according to the instructions of the BCA kit. After being separated by 10% sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE), 30 µg total protein was transferred to cellulose nitrate film and sealed with 5% skim milk at room temperature for 1 h. After incubation with Caspase-3, Bcl-2, cyclinB1, cyclinD1, MMP9, SLPI and GAPDH at 4°C overnight.

HRP-labeled secondary antibody was added to the cellulose nitrate film on the second day, which was incubated at room temperature for 1 h. The protein bands were observed by an enhanced chemiluminescence detection system.

Statistical Analysis

SPSS 23.0 statistical software was applied for statistical analysis and GraphPad Prism 5 was used to make figures. Experimental data are represented as mean ± standard deviation. One-way analysis of variance coupled with Tukey post hoc was used to evaluate intergroup differences. $P < 0.05$ was considered statistically significant.

Results

The Expression of LCN2 and SPLI in Gastric Cancer Cell Lines

The expression of *LCN2* in gastric cancer cell lines (SCG-7901, Fu97, AGS and HST2) was increased compared with that in HGT-1 cells (Figure 1A). Likewise, the expression of *SPLI* in gastric cancer cell lines (SCG-7901, Fu97, AGS and HST2) was increased compared with that in HGT-1 cells (Figure 1B). *LCN2* and *SPLI* showed the highest levels in AGS cells among gastric cancer cell lines, and thus AGS cell line was chosen for the subsequent experiments.

AGS Cells are Transfected

AGS cells were respectively transfected with shRNA-NC, shRNA-*LCN2*-1, and shRNA-*LCN2*-2. The expression of *LCN2* in AGS cells transfected with shRNA-*LCN2*-1/2 was decreased compared with that in the control group and the shRNA-NC group. There was no obvious difference in *LCN2* expression in AGS cells between the control group and the shRNA-NC group (Figure 2A). The changes of *SPLI* in these four groups were consistent with that of *LCN2* (Figure 2B). AGS cells transfected with shRNA-*LCN2*-1 exhibited the lowest level of *LCN2* and *SPLI*, and shRNA-*LCN2*-1 was selected for the follow-up experiments.

Down-Regulation of LCN2 Mediating IL-17 Suppresses the Proliferation and Clone Formation of AGS Cells

The proliferation of AGS cells was not obviously changed by *IL-17*. Down-regulation of *LCN2* mediating *IL-17* suppressed the proliferation of AGS cells. The proliferation of

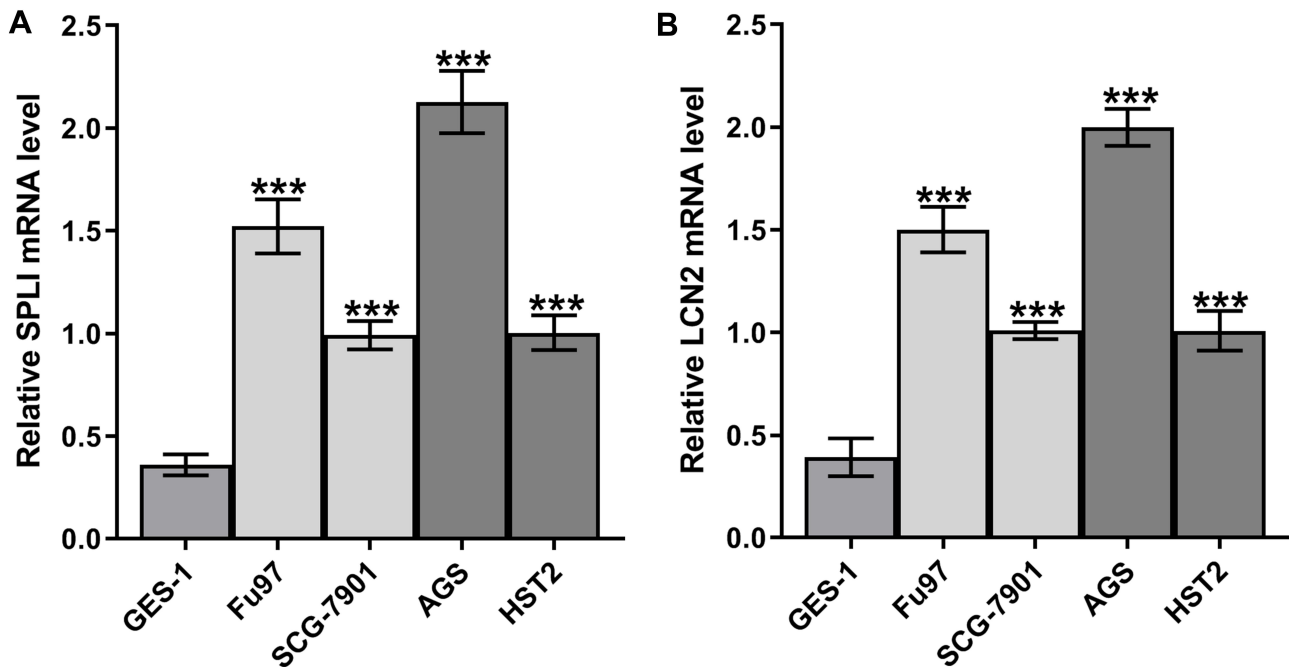


Figure 1 The expression of LCN2 and SPLI in gastric cancer cell lines. (A) SPLI mRNA expression in gastric cancer cell lines was analyzed by RT-qPCR analysis. (B) LCN2 mRNA expression in gastric cancer cell lines was analyzed by RT-qPCR analysis. ***P<0.001 vs HGT-1 group.

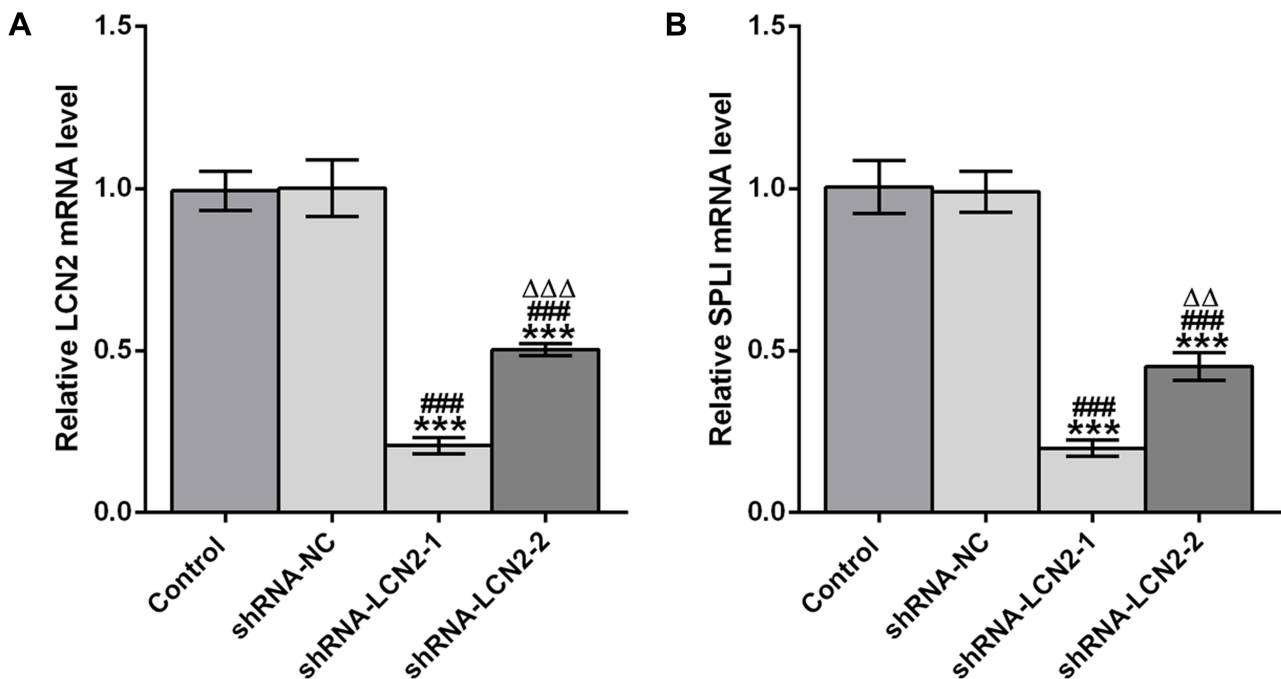


Figure 2 AGS cells are transfected. (A) LCN2 mRNA expression in AGS cells after transfection was analyzed by RT-qPCR analysis. (B) SPLI mRNA expression in AGS cells after transfection was analyzed by RT-qPCR analysis. ***P<0.001 vs Control group. ###P<0.001 vs shRNA-NC group. ΔΔΔP<0.001 vs shRNA-LCN2-1 group.

AGS cells treated with *IL-17* was not obviously changed compared with those treated with *IL-17* and transfected with shRNA-NC (Figure 3A). As shown in Figure 3B, *IL-17* did not affect the clone formation of AGS cells

and shRNA-NC also had no obvious effect on the clone formation of *IL-17*-treated AGS cells. Down-regulation of *LCN2* mediating *IL-17* suppressed the clone formation of AGS cells (Figure 3B).

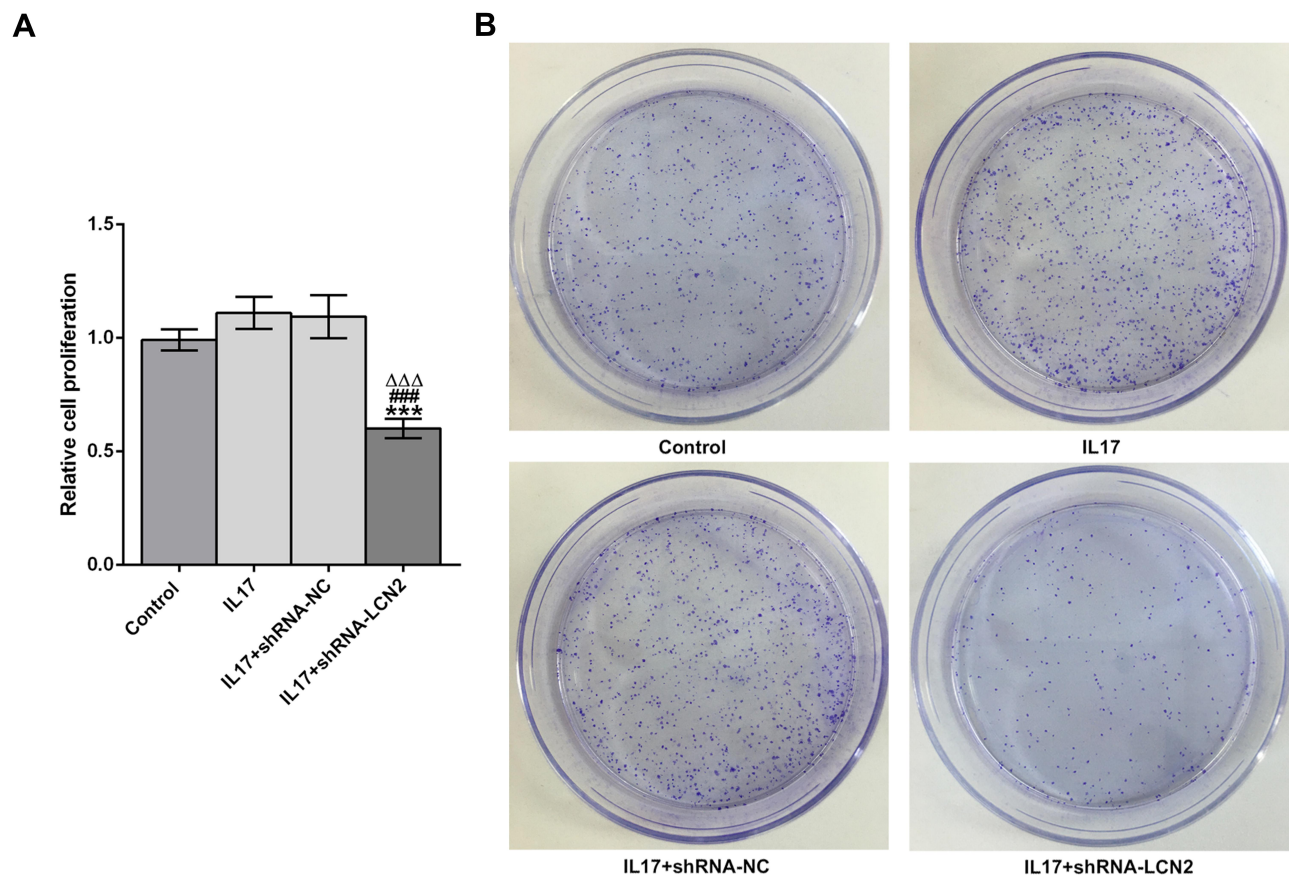


Figure 3 Down-regulation of LCN2 mediated by IL-17 suppresses the proliferation and clone formation of AGS cells. **(A)** The proliferation of AGS cells treated with IL-17 after transfection was detected by CCK-8 assay. $***P<0.001$ vs control group. $####P<0.001$ vs IL17 group. $\Delta\Delta\Delta P<0.001$ vs IL17+shRNA-NC group. **(B)** The clone formation ability of AGS cells treated with IL-17 after transfection was detected by clone formation assay.

Down-Regulation of LCN2 Mediated by IL-17 Suppresses the Migration and Invasion of AGS Cells

IL-17 promoted the migration (Figure 4A) and invasion (Figure 4B) of AGS cells. There is no obvious difference in migration and invasion of AGS cells between the IL-17 group and the IL17+shRNA-NC group. Down-regulation of *LCN2* weakened the promotion effect of *IL-17* on the migration and invasion of AGS cells.

Down-Regulation of LCN2 Mediated by IL-17 Promotes Apoptosis and Suppresses Cell Cycle of AGS Cells

DDP enters into cells and blocks transcription and DNA replication, leading to cell cycle arrest and cell apoptosis.²⁴ In 1965, DDP was confirmed to have a broad-spectrum anticancer effect,²⁵ showing remarkable efficacy in the treatment of various cancers, including lung cancer, ovarian

cancer, and gastric cancer. However, long-term use of DDP in gastric cancer patients will increase the risk of developing drug resistance to it. Therefore, how to treat gastric cancer with DDP resistance is worth studying. *IL-17* had no obvious effect on apoptosis of AGS cells while DDP promoted the apoptosis of AGS cells. *IL-17* suppressed the apoptosis of AGS cells treated with DDP, and down-regulation of *LCN2* mediated by *IL-17* promoted the apoptosis of AGS cells treated with DDP (Figure 5A). *IL-17* did not cause the activation and acceleration of cell cycle of AGS cells, and DDP could induce G2/M arrest and block the G2 phase of AGS cells. The inhibition of DDP on cell cycle was antagonized by *IL-17*, and the antagonistic effect of *IL-17* was reversed by the down-regulation of *LCN2* (Figure 5B).

LCN2 Can Combine with SLPI

When *LCN2* antibody was added to lysates of AGS cells, protein expression of *LCN2* was observed in the

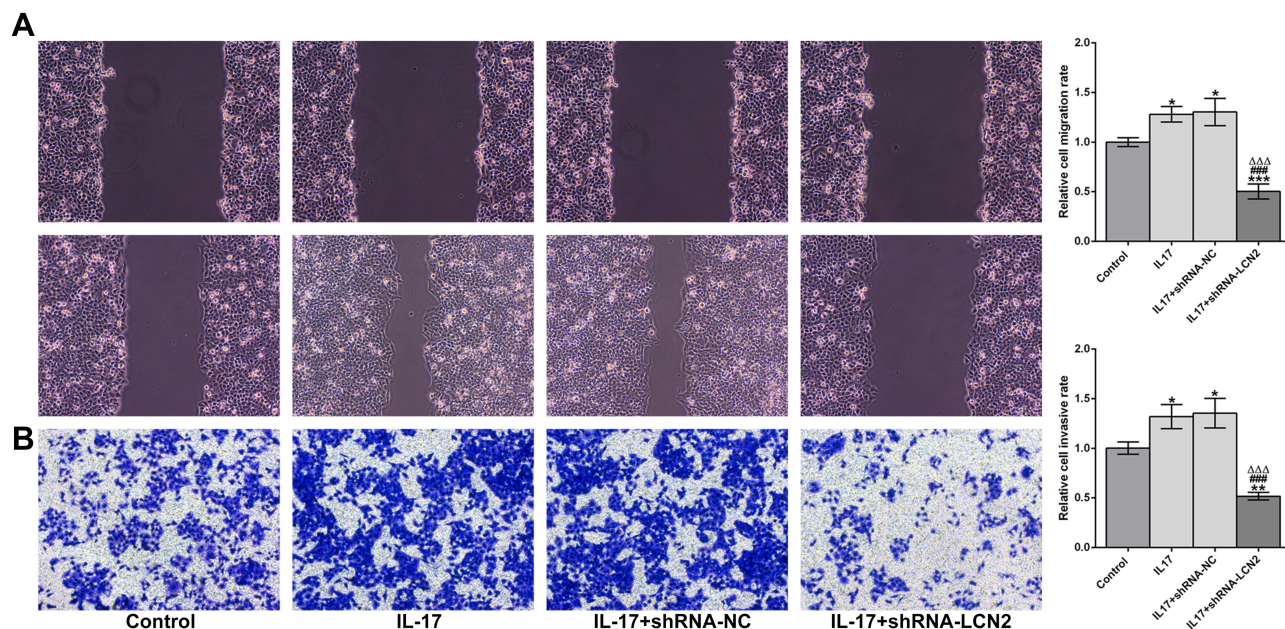


Figure 4 Down-regulation of LCN2 mediated by IL-17 suppresses the migration and invasion of AGS cells. **(A)** The migration of AGS cells treated with IL-17 after transfection was detected by wound healing assay. **(B)** The invasion of AGS cells treated with IL-17 after transfection was detected by transwell assay. *P<0.05, **P<0.01 and ***P<0.001 vs control group. ####P<0.001 vs IL17 group. ΔΔΔP<0.001 vs IL17+shRNA-NC group.

lysates. The protein expression of *SLPI* still existed in lysates of AGS cells added with *LCN2* antibody (Figure 6).

Down-Regulation of LCN2 Affects Cell Phenotype-Associated Proteins in AGS Cells

As shown in Figure 7, *IL-17* promoted the expression of *MMP9* and *Bcl-2* in AGS cells. DDP increased the *Caspase-3* expression and decreased the expression of *Bcl-2*, *cyclinB1*, *MMP9*, and *SLPI* in AGS cells. The expression of *Bcl-2* and *MMP9* was increased in AGS cells treated with DDP and *IL-17*. Down-regulation of *LCN2* promoted the *Caspase-3* expression and suppressed the expression of *Bcl-2*, *cyclinD1*, *MMP9* and *SLPI* in AGS cells treated with DDP and *IL-17*.

Discussion

Gastric cancer is characterized by tumor metastasis and invasiveness. The existing treatments for gastric cancer are relatively limited, and tremendous efforts have been devoted to developing new therapeutic strategies for gastric cancer. In the present study, expression of *LCN2* and *SPLI* was increased in gastric cancer

cells. In addition, down-regulation of *LCN2* mediated by *IL-17* suppressed the proliferation, migration and invasion, and cell cycle of gastric cancer cells by targeting *SLPI*.

Inflammatory response has been described as 1 of the top 10 characteristics of tumors.²⁶ Chronic inflammatory response can damage gastric mucosa and induce the formation of gastric cancer.²⁷ Various inflammatory factors secreted by inflammatory cells promote the occurrence and metastasis of tumors in different ways, so inhibiting inflammatory response is one of the key links in the prevention and treatment of gastric cancer. *IL-17* is a pro-inflammatory cytokine that stimulates the *NF-κB* signaling pathway for the transcription of downstream effectors and promotes cell proliferation and angiogenesis. It is also involved in inflammatory response, which promotes the development of gastric cancer.²⁸ *LCN2* is a downstream protein of the *IL-17/NF-κB* pathway. In this study, *IL-17* has no obvious effect on the proliferation, clone formation ability, apoptosis, and cell cycle of gastric cancer cells, which could be affected by the down-regulation of *LCN2*.

SLPI belongs to the Kazal serine protease inhibitor family and has the ability to regulate cell differentiation and proliferation.²⁹ Relevant studies have shown that

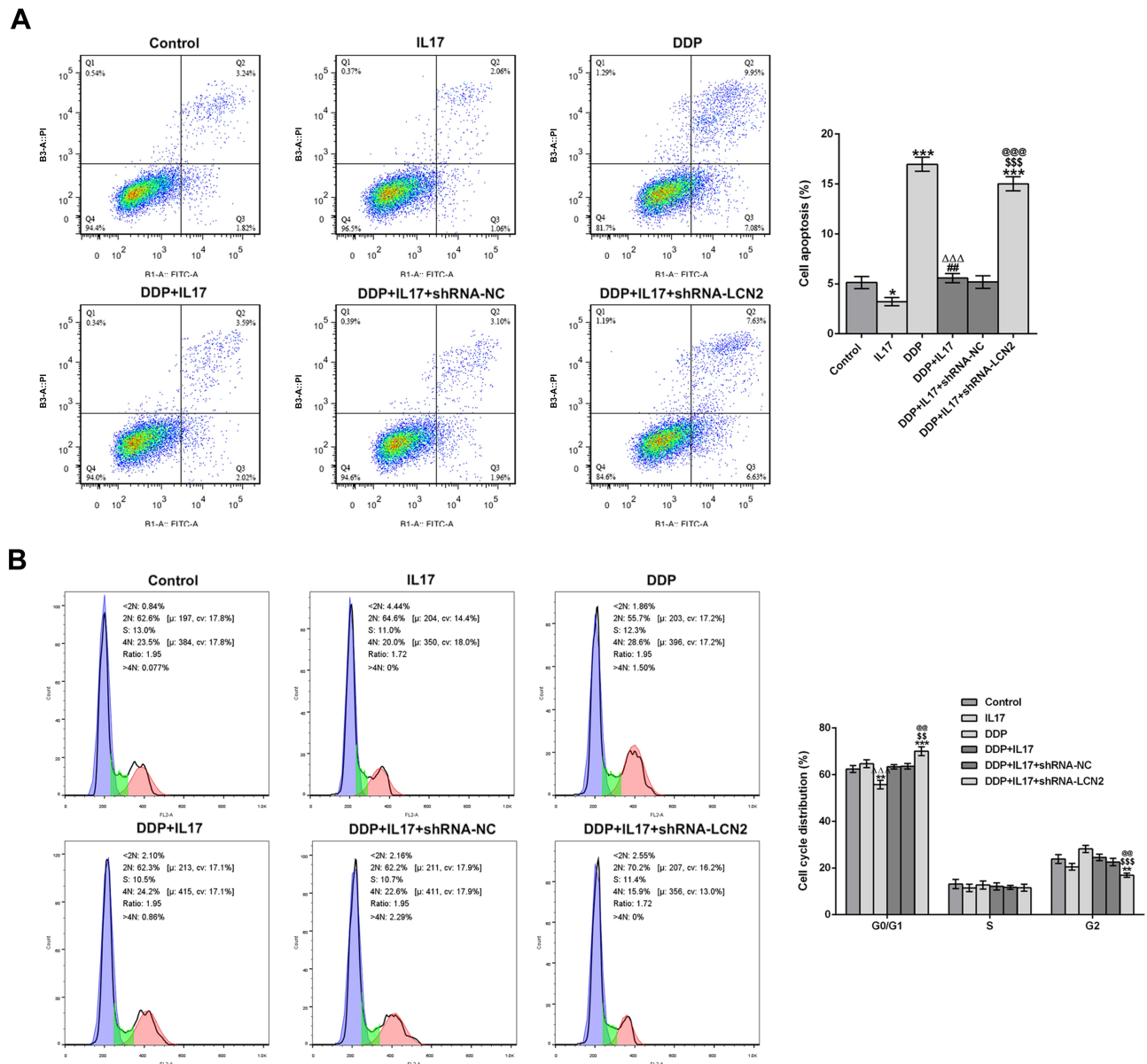


Figure 5 Down-regulation of LCN2 mediating IL-17 promotes apoptosis and suppressed cell cycle of AGS cells. **(A)** The apoptosis of AGS cells treated with IL-17 after transfection was analyzed by flow cytometry analysis **(B)** The cell cycle of AGS cells treated with IL-17 after transfection was analyzed by flow cytometry analysis. * $P < 0.05$, ** $P < 0.01$ and *** $P < 0.001$ vs control group. ## $P < 0.01$ vs IL17 group. ### $P < 0.001$ vs DDP group. $\Delta\Delta\Delta P < 0.01$ and $\Delta\Delta\Delta\Delta P < 0.001$ vs DDP+IL17 group. @ $P < 0.01$ and @@ $P < 0.001$ vs DDP+IL17+shRNA-NC group.

SLPI mRNA and protein were significantly elevated in gastric cancer tissues.^{31,32} *SLPI* expression in ovarian cancer cells was significantly higher than that in normal cells, and thus it was associated with tumor progression.³⁰ Therefore, *SLPI* could be a potentially useful tissue-specific promoter (TSP) for ovarian cancer.³³ *SLPI* inhibition suppressed the proliferation, migration, and invasion of colorectal cancer cells.³⁴ In addition, *IL-17* promoted the DDP resistance of cells in colorectal cancer and ovarian cancer.^{35,36} In this study,

DDP promoted the apoptosis of gastric cancer cells, and *SLPI* expression was decreased accordingly after DDP treatment. *IL-17* up-regulated the *SLPI* expression and antagonized the inhibitory effect of DDP on gastric cancer cells. Down-regulation of *LCN2* could inhibit the proliferation and cell cycle, and could promote the apoptosis of gastric cancer cells by decreasing the *SLPI* expression.

In conclusion, *IL-17* suppressed the proliferation, clone formation, migration, invasion, and cell cycle, and

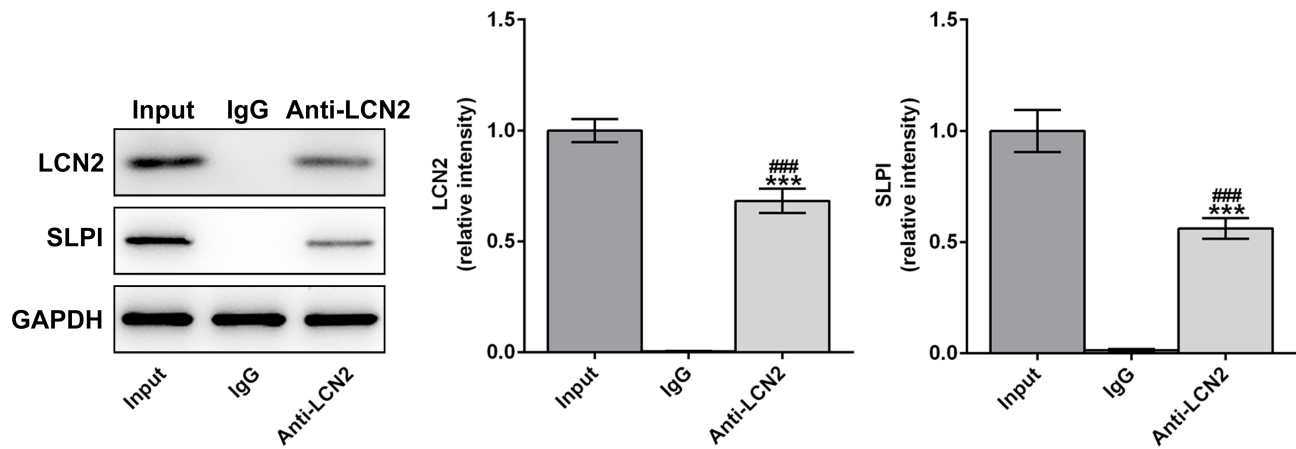


Figure 6 LCN2 can combine with SLPI. The interaction between LCN2 and SLPI was determined by co-immunoprecipitation assay. ***P<0.001 vs input group. ###P<0.001 vs IgG group.

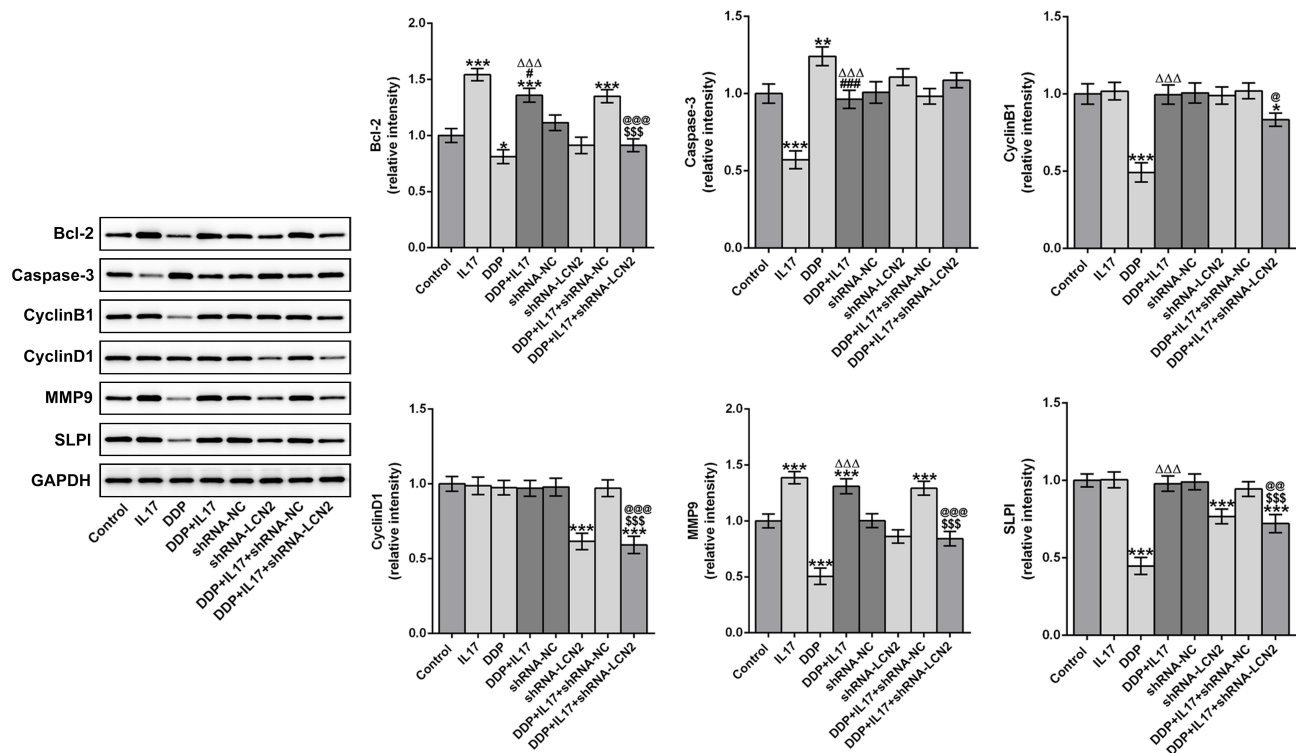


Figure 7 Down-regulation of LCN2 affects cell phenotypic associated proteins in AGS cells. The expression of Bcl-2, Caspase-3, cyclinB1, cyclinD1, MMP9 and SLPI in AGS cells treated with IL-17 and DDP after transfection was analyzed by Western blot analysis. *P<0.05 and ***P<0.001 vs Control group. #P<0.05 and ###P<0.001 vs IL17 group. ΔΔΔP<0.001 vs DDP group. \$\$\$P<0.001 vs DDP+IL17 group. @@@P<0.01 and @@@@P<0.001 vs DDP+IL17+shRNA-NC group.

promoted the apoptosis of AGS cells by down-regulating *LCN2* expression and *SLPI* expression.

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Disclosure

The authors declare they have no conflicts of interest.

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