STAT5A reprograms fatty acid metabolism and promotes tumorigenesis of gastric cancer cells

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Abstract. – OBJECTIVE: The aim of this study was to determine the underlying effect of STAT5A-mediated fatty acid metabolism on the tumorigenesis of gastric cancer cells.

MATERIALS AND METHODS: The expression patterns of STAT5A and FASN in gastric cancer were investigated based on the Cancer Genome Atlas (TCGA) database and compared between 40 pairs of cancer samples and adjacent tissues. The pathological significance of STAT5A in gastric cancer was explored by GESA assay, and the molecular mechanism of STAT5A-mediated FASN expression was investigated by Luciferase assay and ChIP-qPCR. Fatty acid metabolic change was explored by detecting the content of neutral lipid, triglycerides, and phospholipids in STAT5A silenced MKN28 and AGS cells. Furthermore, Cell Counting Kit-8 (CCK-8) assay, colony formation, and Mouse xenograft were used to detect the function of STAT5A-mediated fatty acid metabolism on tumorigenic ability of gastric cancer cells.

RESULTS: Upregulated STAT5A in gastric cancer was found to be not only an unconventional risk for over survival of gastric cancer patients, but also associated with fatty acid metabolism signaling. Furthermore, STAT5A can regulate the expression of the fatty acid binding protein 5 (FABP5) by binding to the promoter of FABP5 in MKN28 and AGS cells. Functional studies have shown that STAT5A-dependent FABP5 expression promoted the proliferation and tumorigenesis of gastric cancer cells by reprogramming intracellular fatty acid metabolism.

CONCLUSIONS: Our results indicate that STAT5A-dependent FABP5 expression plays a carcinogenic role in the tumorigenesis of gastric cancer cells via reprogramming intracellular fatty acid metabolism, which establishes a new mechanism for the tumorigenesis of gastric cancer cells.

Introduction

Although in recent years its global incidence has largely declined, gastric cancer is still one of the main reasons for tumor-related death, due to its poor prognosis[1]. Recent epidemiological data[2,3] have shown that obesity was significantly correlative with the risk of malignant tumors in the population. Clinical evidence-based medical research[4-6] found that excessive body mass index (BMI) or excessive waist circumference was one of the important risks of gastric or esophageal tumors. Although histological staining showed the fat infiltration in gastric cancer tissues[5,7,8], the status of fatty acid metabolism in gastric cancer and its molecular mechanism is still confusing, and there is no study to explore the role of lipid metabolism - on clinical prognosis in gastric cancer.

In mammalian cells, lipid metabolism is strongly associated with fatty acid binding proteins (FABPs), belonging to the intracellular lipid-binding proteins (iLBPs) family and regulating fatty acid uptake, transport, and metabolism[9-11]. Studies[10-12] have shown that FABP5 was a major member of the long-chain fatty acid binding proteins in cells and involved in the activation of the non-classical retinol nuclear receptor PPARβ/δ. Although the mechanism was still unclear, abnormal expression of FABP5 resulted in diseases such as atherosclerosis of the carotid artery and coronary arteries, reflecting its important role in

the cellular fatty acids metabolism[13,14]. Interestingly, FABP5 has been indicated as an oncogene in mammals and was highly expressed in many human cancers[15]. In the MMTV-neu mouse model of breast cancer, tumorigenesis was often accompanied with up-regulation of FABP5[16]. However, the development of tumors can be significantly inhibited by down-regulating FABP5 in these mice[17]. However, the molecular mechanism of FABP5 in tumorigenesis and pathological processes in gastric cancer remains unclear.

Signal transduction and transcriptional activator 5A (known as STAT5A) acts as a nuclear transcription factor that can be activated by inflammatory cytokines or growth factor receptors, not only functioning in many cellular physiological processes, such as immune response and inflammation, but also playing a key role in human cancers[18,19]. Excessive activation of STAT5A caused by self-mutation or hyper-phosphorylation is a key mechanism for malignant proliferation of tumor cells in breast cancer or cervical cancer[20]. Studies[21] have shown that STAT5A was involved in tumor progression by intermediating epithelial-mesenchymal transition. Also, other researches[22] have found that high STAT5A expression was usually associated with poor prognosis in ovarian cancer. Although those results reveal the significance of STAT5A in the pathology of tumors, the role of STAT5A in gastric cancer has not been studied.

The aim of our study was to investigate the expression pattern of STAT5A and its potential functions in gastric cancer. We found that STAT5A can participate in the cellular lipid metabolism process by affecting the expression of FABP5, which further affects the tumorigenesis of gastric cancer cells. These findings define the new physiological functions of STAT5A and provide a theoretical basis for understanding the relationship between tumorigenesis of gastric cancer and cellular fatty acid metabolism.

Materials and Methods

Cell Lines, Reagents, and Antibodies

The human gastric cancer cell lines used in this study (MKN28, MKN45, KATOIII, and AGS) and a normal human gastric mucosal epithelial cell line (GSE1) were purchased from American Type Culture Collection (ATCC, Manassas, VA, USA) and cultured in Roswell Park Memorial Institute-1640 (RPMI-1640) medium supplemented with 10% fetal bovine serum (FBS; Gibco, Grand Island, NY, USA), and 1% penicillin-streptomycin (Gibco, Grand Island, NY, USA). All cells were negative for mycoplasma tested with the MycoProbe Detection Kit (R&D Systems, Minneapolis, MN, USA), and all experiments were repeated at least 3 times with two cell lines.

The plasmids were transfected with liposomal Neofect (Neofect Biotech, Beijing, China) according to the supplier's instructions. A specific primary antibody recognizing FABP5 (ab84028; Abcam, Cambridge, MA, USA), STAT5A (ab32043; Abcam, Cambridge, MA, USA), and glyceraldehyde 3-phosphate dehydrogenase (GAPDH; ab181602; Abcam, Cambridge, MA, USA) was purchased from Abcam (Cambridge, MA, USA).

Clinical Specimens

After obtaining the informed consent from 40 randomly selected gastric cancer patients who did not receive chemotherapy or radiotherapy, their gastric cancer tissues and para-cancer tissues were collected by surgery. This investigation was approved by the Research Ethics Committee of Taizhou People's Hospital (Jiangsu, China).

Immunohistochemical Staining

The human gastric cancer tissue fixed in formalin was made into - section (3-5 μm) in a paraffin-embedded state. Then, the deparaffinized and rehydrated sections were boiled in 10 mM citrate buffer (pH 6.0) for 5 min for antigen retrieval. 3% hydrogen peroxide in methanol was used to inactivate endogenous peroxidase for 10 min at room temperature, followed by blocking with 5% bovine serum albumin (BSA). After incubation with primary antibody for 1 h at 37°C, protein expression in tissues was detected using diaminobenzidine (DAB) labeled secondary antibodies according to the manufacturer's protocol. The staining results were imaged using a Leica microscope and the expression levels of STAT5A in 40 gastric cancer tissues were scored.

Virus Packaging and Infection

The packaging plasmid pMDLg/pRRE, pCMV-VSVG, and the pRSV-REV plasmid containing specific shRNA targeting STAT5A or FABP5 were co-transfected into 293T cells. The supernatant of the 293T cells containing the virus was collected and centrifuged at 32000 g to prepare a concentrated virus suspension. Once infected with indicated virus for 24 h, MKN28 and AGS cells were screened with G418 (Geneticin, 800 ng/

mL) for 1 week to obtain a cell line stably knocking down the targeted gene.

Dual-Luciferase Reporter Gene Assay

Plasmids carrying firefly Luciferase and different-fragments of the FABP5 promoter or pGL3 vectors were co-transfected into MNK28 and AGS cells with plasmid expressing STAT5A and the plasmid pRL-TK carrying *Renilla* Luciferase. After 48 h of transfection, Luciferase activity was detected using a Dual-Luciferase reporter assay kit (Promega, Madison, WI, USA) according to the manufacturer's instructions. All experiments were performed in triplicate and the data are expressed as mean ± SD (Standard Deviation).

Quantitative Real-Time PCR Analysis

Total RNA in the tissues freeze in liquid nitrogen or indicated cells was extracted with TRIzol reagent (Invitrogen, Carlsbad, CA, USA) according to the manufacturer's protocol. After detecting the quality and concentration of the extracted RNA by Nano-Drop 2000 system, 2 µg total RNA was reverse-transcribed into cDNA with a reverse transcriptase kit (TOYO-BO, Osaka, Japan). The mRNA levels of the targeted genes were detected with the SYBR (Synergy Brands) green method (TOYOBO, Osaka, Japan). The data represents two independent experiments with three technical replicates for each set of experiments. The GAPDH gene mRNA transcription level was used as an internal reference for each sample. The primers used in this study were shown in Table I.

Quantification of Neutral Lipid

To detect neutral lipids in gastric cancer cells, the neutral lipid content in MKN28 and AGS cells was measured with the lipophilic fluorescent dye BODIPY 493/503 (Invitrogen, Carlsbad, CA, USA) according to the manufacturer's instructions.

Quantification of Triglycerides and Phospholipids

According to the manufacturer's instructions, cellular phospholipid assay kit (Invitrogen, Carlsbad, CA, USA) and triglyceride assay kit (Invitrogen, Carlsbad, CA, USA) were used to quantify the content of triglyceride or phospholipid in MKN28 and AGS cells. All experiments were performed in triplicate and the data are expressed as mean ± SD.

Clonal Formation

Cells (1000 cells/well) were seeded in 6-well plates. After the clones were enough to be visible, the medium was discarded and the clones were fixed with 4% formaldehyde solution for 10 min, following staining with 0.2% crystal violet for 15 min. Three replicate wells were set for each experimental group.

Cell Viability Assay

Cell viability of different cell lines was determined by cell counting kit-8 (CCK-8) kit (Biotool, Kirchberg, Switzerland). Equal numbers of different genotype cells were incubated in 96-well plates for 24 h. The medium was then replaced with medium containing 10% CCK-8 and incubation continued for 1 h. OD450 was measured using a microplate reader [Multiskan FC, Thermo Fisher Scientific (Waltham, MA, USA)]. The measurement was continued for 3 days, and each set of experiments was repeated 3 times.

Mouse Xenograft

5.0×10^6 stable FABP5-KD or FABP5-KD/STAT5A-OE cell lines and control cells were resuspended in phosphate-buffered saline (PBS), and Matrigel (BD Biosciences, San Jose, CA, USA) was mixed in samples in a 1:1 ratio (v/v). The indicated cells were injected subcutaneously

Table I. Primers used for qPCR.

| Gene	Primers (5′ to 3′, forward/reverse)
STAT5A mRNA	GCAGAGTCCGTGACAGAGG/CCACAGGTAGGGACAGAGTCT
FABP5 mRNA	TGAAGGAGCTAGGAGTGGGAA/TGCACCATCTGTAAAGTTGCAG
FASN mRNA	AAGGACCTGTCTAGGTTTGATGC/TGGCTTCATAGGTGACTTCCA
ACC1 mRNA	GCTCCTTGTCACCTGCTTCT/CAAGGCCAAGCCATCCTGTA
ACOX1 mRNA	GGCGCATACATGAAGGAGACCT/AGGTGAAAGCCTTCAGTCCAGC
CPT1A mRNA	CTGGACAATACCTCGGAGCC/AACGTCACAAAGAACGCTGC
GAPDH mRNA	GGAGCGAGATCCCTCCAAAAT/GGCTGTTGTCATACTTCTCATGG
FABP5 promoter	GAGGAGCAGAAGGTCAGGGAG/CGGGCGAGTCCCTGCTTGCAG
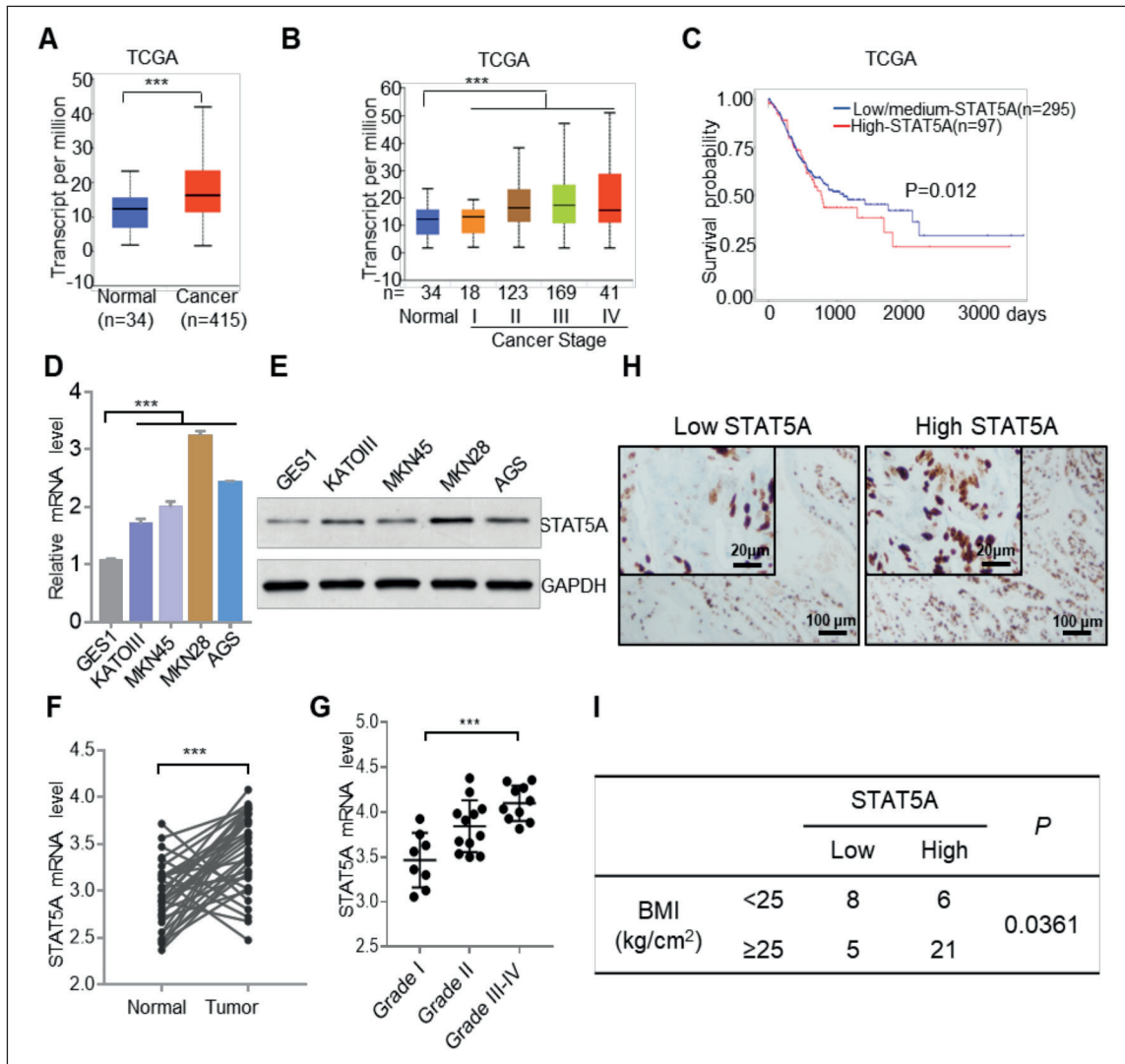
Figure 1. Expression pattern of STAT5A in gastric cancer. **A,** Expression lever of STAT5A in primary gastric cancer (Cancer) compared to normal tissue (Normal) in TCGA dataset. **B,** STAT5A mRNA expression levers in four different stages of gastric cancer based on TCGA dataset. **C,** Overall survival of patients with gastric cancer was calculated using Kaplan-Meier analysis according to the STAT5A mRNA expression lever. **D-E,** Relative mRNA and protein expression level of STAT5A in four gastric cancer cell lines compared to GES1 cells. GAPDH served as endogenous control. **F,** STAT5A mRNA expression pattern in 40 pairs of human gastric cancer tissues (Cancer) and adjacent tissues (Normal). **G,** STAT5A mRNA expression lever in four different grades of 40 cancer samples. **H,** Representative IHC image show STAT5A expression pattern in gastric cancer tissues (magnification 100X and 600X). I, Correlation of STAT5A expression and BMI was statistically analyzed with Chi-square test.

into the back of 5 weeks old male BALB/C nude mice. Tumor growth size was measured every 3 days when palpable tumor-like products were produced (about 4 mm in diameter) and tumor growth curves were plotted. Four weeks later, the mice were sacrificed and tumors were harvested for further analysis. All protocols were approved by the Institutional Animal Ethics Committee.

Statistical Analysis

Statistical analysis of the data in this study was performed using SPSS 21.0 software (Version X; IBM, Armonk, NY, USA), and plots were drawn with GraphPad prism 7.0 (Version X; San Diego, CA, USA). The distribution differences of quantitative data were analyzed with one-way ANOVA or two-sided t-test, and Bonferroni test was used

to validate ANOVA for pairwise comparisons. The relationship between STAT5A expression and BMI was detected by χ^2-test. $p < 0.05$ was considered as statistically significant.

Results

Expression Pattern of STAT5A in Gastric Cancer

To explore the potential role of STAT5A in the pathogenesis of gastric cancer, the expression pattern of STAT5A was first analyzed. The TCGA database showed a raising mRNA expression level of STAT5A in gastric cancer compared to adjacent tissues (Figure 1A). After classifying these gastric cancers, it was found that STAT5A expression increased with the pathological stages (Figure 1B). Patients with high STAT5A expression showed worse survival than those in low STAT5A expressed patients (Figure 1C). To further validate the expression pattern of STAT5A in gastric cancer, STAT5A expression was compared in four gastric cancer cell lines and normal gastric cell lines (GSE1). The results showed that STAT5A expressing in gastric cancer cells was higher than that in GSE1, and STAT5A expressing in MKN28 and AGS cells was the most evident.

Further, the expression of STAT5A in 40 clinically collected cancer tissues and adjacent tissues was compared. In parallel, STAT5A expressing in gastric cancer tissues was significantly raised compared to adjacent tissues (Figure 1F, **Supplementary Table SI**). Considering clinical grading of gastric cancer, the average expression level of STAT5A in high tumor grades (grade III-VI) was found significantly higher than that in lower tumor grades (grade I and II; Figure 1G).

To further clarify STAT5A protein expression pattern in clinical gastric cancer tissues, we performed IHC staining of STAT5A in 40 gastric cancer tissues, and found that STAT5A was mainly expressed in the nucleus of gastric cancer cells (Figure 1H). To analyze the relationship between STAT5A expression and clinical characteristics of patients with gastric cancer, we found a significant relationship between STAT5A expression and body mass index (BMI) in gastric cancer patients (χ^2-test, p=0.0361; Figure 1H). To be more specific, 52.5% (21/40) of patients were overweight (BMI>25) and high expression of STAT5A in gastric cancer tissues, while 72.5% (29/40) patients showed consistent feature of BMI

and STAT5A expression (Figure 1I). These results demonstrated that STAT5A expression in gastric cancer tissues was associated with patient BMI.

STAT5A Function on Fatty Acid Metabolism in Gastric Cancer Cells

Numerous studies[23-25] have indicated the key function of fatty acid metabolism in tumorigenesis, and the above results showed that the expression pattern of STAT5A in gastric cancer tissues is associated with BMI. Therefore, we sought to further verify whether STAT5A was involved in fatty acid metabolism in gastric cancer. Based on data from GSE69306, STAT5A was significantly associated with fatty acid metabolism pathways (NES value = 1.15, $p < 0.001$; Figure 2A). Moreover, Kaplan-Meier survival plot showed gastric cancer patients with BMI $\geq$ 25 kg/m^2 showed a poor survival prognosis (Figure 2B). It is speculated that STAT5A was involved in the regulation of fatty acid metabolism and combined the fatty acid metabolic signaling pathway with STAT5A may function in the development and progression of gastric cancer.

To assess whether STAT5A was involved in reprogramming fatty acid metabolism in gastric cancer cell lines, we examined the expression of several key fatty acid metabolic enzymes enriched in the fatty acid metabolism pathway of GSE69306 in STAT5A knockdown cells, and the results showed that FASN, ACOX1, CPT1A, ACC1, and FABP5 mRNA expression levels were down-regulated in STAT5A knockdown MKN28 and AGS cells. Surprisingly, FABP5 mRNA levels showed the greatest change, and exogenous overexpression of STAT5A can significantly rescue FABP5 expression (Figure 2C).

Further, we measured the effect of STAT5A expression on the content of fatty acids and their metabolic intermediates in gastric cancer cells. Our data showed that knockdown STAT5A in MKN28 and AGS cells resulted in a significant decrease in intracellular triglycerides and phospholipids levels, whereas restoring STAT5A expression increased the levels of triglycerides and phospholipids in MKN28 and AGS cells (Figure 2D, 2E). Moreover, cellular staining confirmed the content of neutral lipids in MKN28 and AGS cells were significantly reduced by silencing STAT5A, while exogenous expression STAT5A restored the cellular content of neutral lipids to a certain degree (Figure 2F). These results indicated that STAT5A had a potential effect on the expression of fatty acid metabolism-related enzymes, which
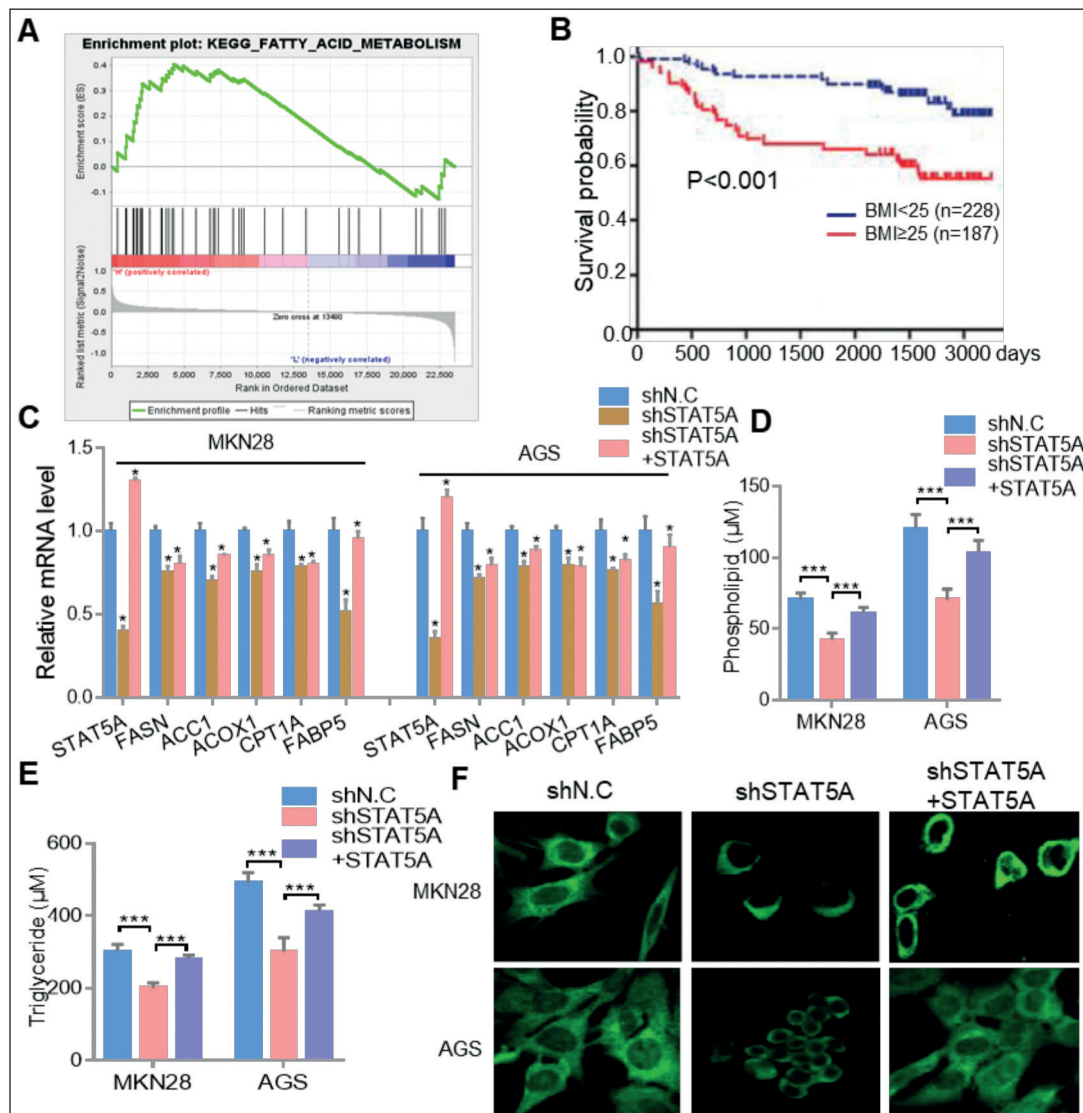
Figure 2. STAT5A function on fatty acid metabolism in gastric cancer cells. **A,** Identification of gene sets enriched in phenotypes correlated with STAT5A by GSEA with GSE69306 data. **B,** Kaplan-Meier survival curves showed poor over survival with BMI≥25 (kg/m²). **C,** RT-qPCR analysis for mRNA levels of the key lipid metabolic enzymes FASN, ACC1, ACOX1, CPT1A, and FABP5 in the indicated cells. **D-E,** Cellular content of phospholipids **(D)** and triglycerides **(E)** was detected in the indicated cells. F, The neutral lipids content was detected by double staining with BODIPY 493/503 dye in the indicated cells (magnification 600X).

further affected the levels of fatty acids and their metabolic intermediates in gastric cancer cells.

STAT5A Dependent FABP5 Expression Mediates Fatty Acid Metabolism in Gastric Cancer Cells

To confirm that STAT5A has a potential effect on the expression of FABP5 in gastric cancer cells, we first explored the relationship of FABP5 and STAT5A expressed in gastric cancer. The results showed that the mRNA expression level of FABP5 in gastric cancer tissues was significantly higher than that in normal tissues (Figure 3A, **Supplementary Table SII**). Moreover, the expression level of FABP5 in gastric cancer had a significant positive correlation with STAT5A (Figure 3B). FABP5 expression was significantly downregulated in the stable STAT5A knockdown MKN28 and AGS cells, but FABP5 level was also up-regulated after exogenous overexpression of STAT5A (Figure 3C). Those disclosed that STAT5A can regulate FABP5 expression in gastric cancer cells.

To explore how STAT5A regulated FABP5 expression in gastric cancer, we tested whether STAT5A bind to the promoter of the FABP5 gene. Truncates of the FABP5 promoter region were cloned into vectors containing the Luciferase reporter gene (Figure 3D). By measuring the
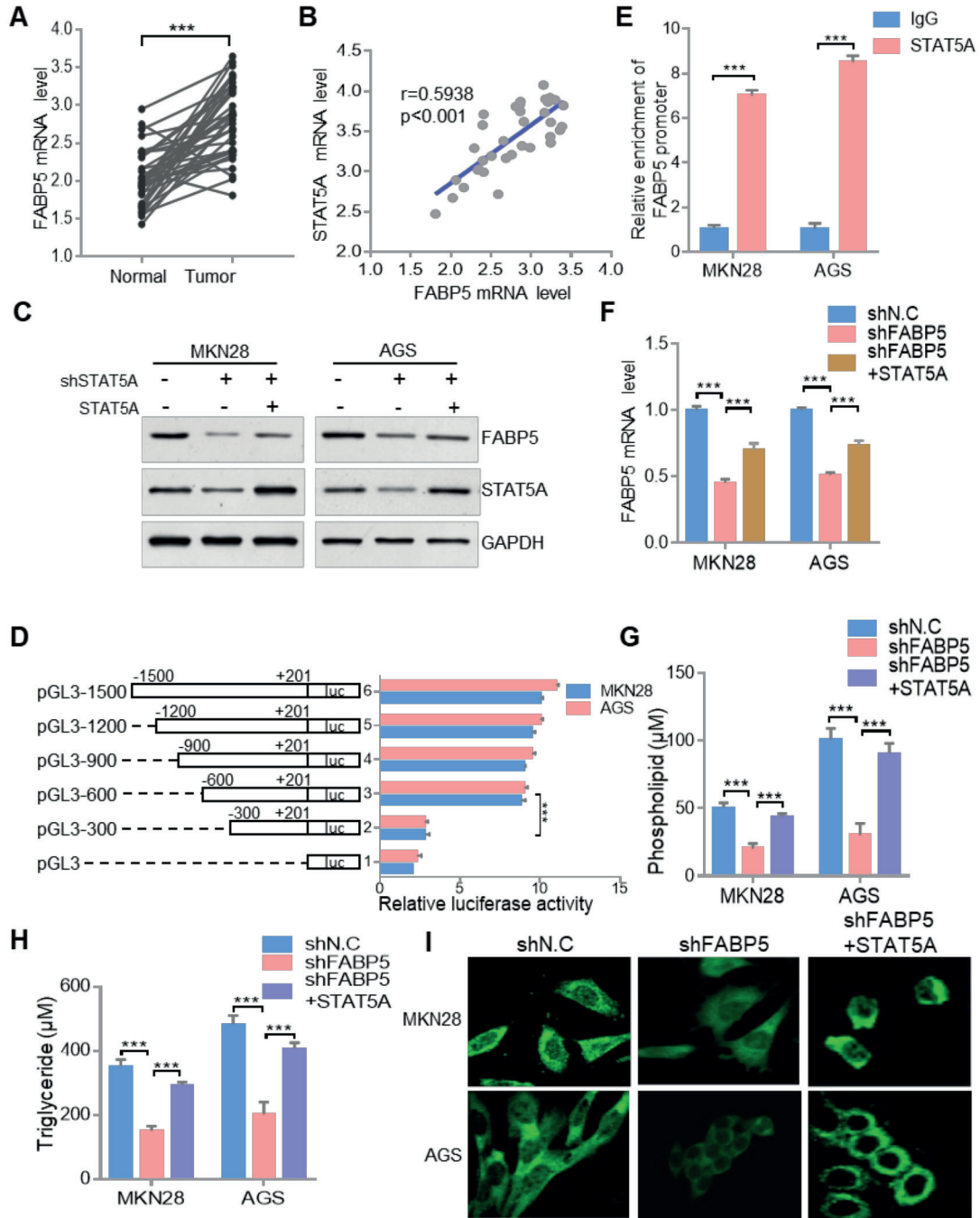

Figure 3. STAT5A dependent FABP5 expression mediates fatty acid metabolism in gastric cancer cells. **A,** Expression lever of FABP5 mRNA in gastric cancer contract to normal tissues. **B,** FABP5 co-expressed with STAT5A in gastric cancer based on 40 gastric cancer tissues. **C,** Relative protein expression of FABP5 in the indicated cells. **D,** FABP5 promoter deletions fused to the Luciferase reporter gene were transfected with STAT5A in MKN28 and AGS cell lines. **E,** ChIP assay was used to examine the interaction of FABP5 promoter with STST5A in MKN28 and AGS cell lines. **F,** Relative mRNA expression of FABP5 in the indicated cells. **G-H,** The levels of phospholipids (**G**) and triglycerides (**H**) were measured in the indicated cells. **I,** The neutral lipid content was detected by double staining with BODIPY 493/503 dye in the indicated cells (magnification 600 ×).
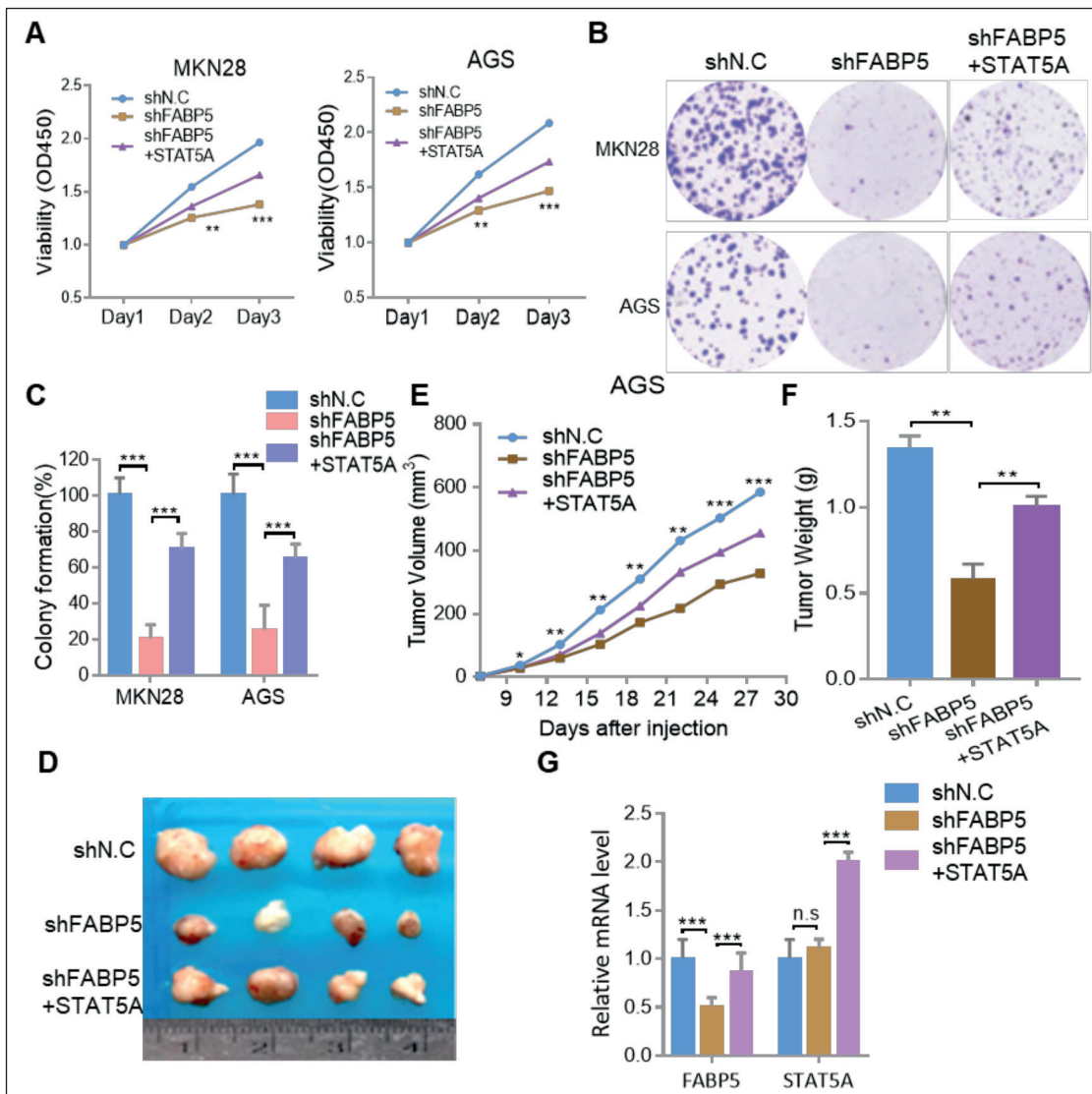
Figure 4. STAT5A-regulated fatty acid metabolism promotes tumorigenic ability of gastric cancer cells *in vitro* and *in vivo*. **A,** CCK8 assay showed cells viability in the indicated cells. **B,** Colony formation assay showed cell growth of the indicated cells (magnification 20X). **C,** Qualification of the colony formation shown in B (n=3). **D,** The representative pictures of dissected tumors from nude mice transplanted with stable FABP5-KD or FABP5-KD/STAT5A-OE AGS cells. **E,** Subcutaneous tumor growth curves of mice in different treatment groups was presented. **F,** The average weight of tumors at the time the animals were sacrificed in the indicated groups. **G,** Relative mRNA expression pattern of associated gene in tumor tissue acquired from nude mice.

Dual-Luciferase reporter gene expression, overexpression of STAT5A was found to increase the reporter gene expression, and when we intercepted the upstream of the FABP5 promoter by approximately 300 bp, the reporter gene expression intensity was significantly reduced (Figure 3D). Therefore, we hypothesized that approximately 300 bp upstream of the FABP5 promoter are sufficient as a binding site for STAT5A. In addition, the ChIP-qPCR assay indicated that STAT5A was

able to significantly enrich the 300 bp upstream of the FABP5 gene promoter (Figure 3E). Those results indicated that STAT5A was a transcription factor of FABP5 in gastric cancer cells.

To further investigate the effect of STAT5A-dependent FABP5 transcription on fatty acid metabolism in gastric cancer cells, we constructed a stably knock down FABP5 MKN28 and AGS cell line, and exogenously expressed STAT5A in this cell line can restore the expres-

sion level of FABP5 to some extent (Figure 3F). By measuring the levels of fatty acids and their metabolites in those cell lines, we found that knockdown FABP5 significantly down-regulated the levels of triglycerides and phospholipids in MKN28 and AGS cells, while restoring STAT5A rescued intracellular levels of triglycerides and phospholipids (Figure 3G, 3H). This result was consistent with the staining result of neutral lipids in MKN28 and AGS cells (Figure 3I). These results indicated that STAT5A can affect fatty acid metabolism by regulating the expression of FABP5 in gastric cancer cells.

STAT5A-Regulated Fatty Acid Metabolism Promotes Tumorigenic Ability of Gastric Cancer Cells

To assess whether STAT5A-mediated FABP5 expression has an effect on the tumorigenic capacity of gastric cancer cells via regulating fatty acid metabolism, we next investigated the effect of STAT5A-regulated FABP5 expression on the proliferation of gastric cancer cells *in vitro*. In the MKN28 and AGS cell lines that have been constructed stably knock down FABP5, the CCK-8 assay showed that silencing FABP5 significantly down-regulated cell viability, but cell viability increased significantly after overexpression of STAT5A (Figure 4A). Consistent with this, knockdown FABP5 significantly reduced the colony formation of gastric cancer cells, whereas more clones were observed after overexpression of STAT5A (Figure 4B, 4C). Therefore, the above results can be inferred that STAT5A-regulated FABP5 expression has the positive effort on the proliferation of gastric cancer cells via mediating fatty acid metabolism.

Next, we explored the effect of STAT5A-mediated fatty acid metabolism on the tumorigenesis of gastric cancer cells *in vivo*. A stable FABP5 silenced AGS cell line was selected as a representative to explore the tumorigenesis in a xenograft mouse model. Interestingly, the result of xenograft tumor model displayed that silencing FABP5 not only significantly down-regulated tumor growth rate, but also weakened the size and weight of the tumor formation, while overexpression of STAT5A significantly up-regulated tumor growth rate, size, and weight (Figure 4D, 4E, 4G). Therefore, the above results indicated that STAT5A-regulated fatty acid metabolism promotes tumorigenic ability of gastric cancer cells *in vivo* via raising the expression of FABP5.

Discussion

The association between metabolism and the development and treatment of cancer has been described in a number of cancer studies. Further, Aleman et al[26] showed that controlling the incidence of obesity is increasingly recognized as an important measure to reduce cancer risk. With the progress in cancer research, the relationship between fatty acid metabolism and cancer development and treatment has also been intensively explored, which further increased our understanding of their connection[27]. Fatty acid metabolism was also recognized to play a key role in the initiation, progression, and drug resistance of cancer[28]. To date, many obesity-related drugs [lipid-lowering (statin) or anti-diabetic (metformin)] have been found to be a better therapeutic effect on cancer[29,30]. Collectively, these observations further suggested that studies[31] about lipid metabolism in tumor cells may be a viable strategy to address cancer development, progression, and drug resistance.

Our research found that fatty acid metabolism in gastric cancer cells can also significantly affect the tumorigenic ability of gastric cancer cells. The down-regulation of fatty acid binding protein 5 can significantly reduce the tumorigenic ability of gastric cancer cells *in vivo* accompanying with the reducing content of fatty acids in the cells. Therefore, in the future, further exploration of lipid metabolism in gastric cancer will provide a new dawn for the treatment of gastric cancer.

STAT5A was widely recognized as a tumor-promoting gene in tumors[32]. STAT5A has been recognized as transcription factor that promotes the proliferation, differentiation, and the pathogenesis of tumors, and this has been emphasized in some breast cancer models[33]. In the WAP-TAg mouse model of breast cancer, the STAT5A hemizygous mice sufficiently resulted with a less, smaller, and delayed tumor formation than the wild type mice[34]. Furthermore, in a mouse model overexpressing STAT5A, mice were more susceptible to tumors[35]. These studies indicated that abnormal expression of STAT5A was an important factor in the progression of tumor pathology.

In this research, we sought to clarify the specific function of STAT5A in the pathogenesis of gastric cancer and its molecular mechanism. We not only found that STAT5A was up-regulated in gastric cancer, but STAT5A can significantly affect the fatty acid metabolism pathway in gastric cancer cells, which was a new discovery of

STAT5A in the field of cancer research. In addition, except for fatty acid metabolism pathways, we also found that STAT5A significantly enrich glucose-related pathways, such as "fructose and mannose metabolism", "pentose and glucuronate interconversions", and "starch and sucrose metabolism" pathway. This evidence fully demonstrated the important role of STAT5A in the field of tumor metabolism. In conclusion, a more in-depth understanding of how STAT5A activity is regulated in gastric cancer will bring new dawn to the treatment of gastric cancer.

Conclusions

In summary, our study described a novel mechanism of STAT5A on the fatty acid metabolism of gastric cancer. In addition, we demonstrated for the first time that STAT5A can significantly affect the tumorigenic ability of gastric cancer cells by regulating the expression of FABP5 in gastric cancer, and confirmed that the up-regulated STAT5A plays a cancer-promoting function in the pathological process of gastric cancer. Besides, it provides a new perspective for STAT5A in cancer research.

Conflicts of interest
The authors declare no conflicts of interest.

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