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Original Research Article

Mesenchymal stem cells facilitate gastric cancer cell growth and oxaliplatin resistance via upregulation of SMARCA5

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Abstract

Purpose: *To evaluate the role of mesenchymal stem cells (MSCs) in gastric cancer (GC), and reveal its underlying mechanisms.*
Methods: *Expression of SMARCA5 was quantified in GES-1, AGS and MKN45 cell lines. In MSCs-GC co-cultured cells, cell viability was assessed using cell counting kit-8 (CCK-8) assay, and colony formation were performed to determine cell proliferation. The invasion of the MSCs-GC cells was evaluated by Transwell assay. The levels of vimentin, snail and slug, as well as Wingless-Int (Wnt)/β-catenin related proteins β-catenin, Axin, c-myc, and matrix metalloproteinase (MMP)-7 were determined using immunoblotting. Oxaliplatin was added to GC cells, and the effect of siSMARCA5 on cell sensitivity to oxaliplatin was investigated after transfection with SMARCA5 siRNA into MSCs-GC cells.*
Results: *SMARCA5 was highly expressed after co-culture with MSCs ($p < 0.001$). The MSCs facilitated the proliferation of GC cells, and enhanced cell invasion as well as migration ($p < 0.001$) compared with untreated cells. MSCs also promoted epithelial–mesenchymal transition (EMT) by increasing production of vimentin, snail, and slug ($p < 0.001$). The MSCs decreased the sensitivity of GC cells to oxaliplatin, while the knockdown of SMARCA5 reversed the effect ($p < 0.001$). Furthermore, MSCs up-regulated β-catenin, c-myc, and MMP-7 levels, but downregulated Axin expression compared with untreated cells ($p < 0.001$). However, siSMARCA5 blocked these processes compared with si-NC group ($p < 0.001$).*
Conclusion: *MSCs facilitate GC cell growth and oxaliplatin resistance by upregulating SMARCA5 and activating Wnt/β-catenin signaling. This may provide an alternative treatment target for patients with GC.*

Keywords: *Mesenchymal stem cells, Gastric cancer, SMARCA5, Wingless Int/β-catenin*

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INTRODUCTION

Gastric cancer (GC) is the fifth most commonly diagnosed malignancy and is responsible for over 1 million new diagnoses every year, and it is the third deadliest cancer globally [1]. Clinically, surgery is the choice for patients with early GC, while advanced GC patients with distant

metastases or recurrence may benefit from chemotherapy, radiation, or immunotherapy. However, a poor general condition or resistance to drugs usually contributes to treatment failures. Mesenchymal stem cells (MSCs) possess the multi potential to differentiate into various mesenchymal lineages such as osteoblasts, adipocytes, chondrocytes, and myocytes [2]. The MSCs are involved in cell proliferation, cell homing or migration, and immunosuppressive function. It has been suggested that MSCs are essential in tumorigenesis [3]. A previous study has shown that a hybrid of MSCs and GC cells could facilitate proliferation, migration, and stemness [4]. Moreover, it has been reported that MSCs promote the acquisition of stem cell properties in cancer cells, thereby conferring chemoresistance to cancer cells. Previous studies have confirmed that MSCs enhance cancer cell chemoresistance *in vitro* and *in vivo* [5].

The SMARCA5, also called human sucrose non-fermenting protein 2 homologue, play a pivotal role in gene expression, DNA replication, and repair, as well as maintenance of higher-order chromatin structure. Besides, it has been reported that SMARCA5 is an oncogene in diverse cancers. A study has revealed that aberrant SMARCA5 contributes to breast cancer cell proliferation and migration, which leads to a poor prognosis [6]. Another study reported that SMARCA5 is highly expressed in non-small cell lung cancer (NSCLC), and facilitates cancer cell proliferation and invasion [7]. Recently, it was suggested that miR-146a–POU3F2 / SMARCA5 pathway is crucial in inhibiting glioblastoma-stemness and promoting temozolomide response, indicating that this pathway may serve as a novel therapeutic target in glioblastoma [8]. However, the role of SMARCA5 in GC remains unclear.

Therefore, MSCs were co-cultured in GC cells in this study, and cell proliferation, invasion, migration, and sensitivity to oxaliplatin were measured, followed by determination of Wnt / β-catenin pathway.

EXPERIMENTAL

Cell culture and co-culture system

The human gastric epithelial GES-1, GC AGS, and MKN45 cell lines were obtained from American Type Culture Collection (Manassas, USA), while human MSCs were bought from Cyagen Biosciences (Guangzhou, China). The cells were maintained in RPMI-1640 medium (Gibco, USA) by adding 10 % fetal bovine serum (FBS, Gibco, USA), and 1 % penicillin-streptomycin at 37 °C in 5 % CO_2.

The MSCs were mixed with AGS and MKN45 cells, and co-cultured cells could adhere to the plate. Then GC cells in the co-culture system were incubated in DMEM containing 10 % heat-inactivated FBS at 37 °C in 5 % CO_2.

Cell transfection

The SMARCA5 siRNA (siSMARCA5) and negative control siRNA (siNC) were purchased from GenePharma (Shanghai, China). Next, siSMARCA5 transfection into AGS and MKN45 cells was conducted using Lipofectamine 2000 (Invitrogen, USA) for 48 h, in accordance with manufacturer's instructions. When transfection was completed, the cells were used for further experiments.

Cell viability assessment

Cell viability was assessed using a cell counting kit-8 (CCK-8) assay kit (Yeasen Biology, China) in line with the manufacturer's instructions. After transfection of siSMARCA5 for 48 h, co-cultured cells (5×10^3 cells/well) were inoculated into 96-well plates, followed by adding 10 µL CCK-8 reagents. The absorbance was measured at 450 nm using a microplate reader (Bio-Rad Laboratories, Richmond, CA).

Flow cytometry

Cell apoptosis was assessed by double-staining the cells with Annexin V-FITC followed by propidium iodide (PI). Then the cells (300,000 per well) were seeded in 6-well plates and treated with MSCs, oxaliplatin, and si-SMARCA5, and thereafter stained with 5 µL FITC-conjugated annexin V and 5 µL of PI for 15 min at room temperature in the dark. Apoptotic cells were quantified by flow cytometry using a CytoFlex cytometer (Beckman Coulter). Cells positive for Annexin V only were considered early apoptotic; cells positive for PI only were considered necrotic, while double positive cells were taken as late apoptotic cells.

Transwell assay

The invasiveness and migration of MSCs-GC cells were evaluated using Transwell assay. The MSCs-GC cells (1×10^5 cells) in serum-free culture medium were seeded on the top chamber (8-µm pore size, Corning) and incubated at 37 °C in 5 % CO_2. For invasion assay, the upper chamber was coated with 100 µL of Matrigel (3.9 µg/µL) and then incubated at 37 °C for 30 min for

gelation. The complete DMEM/F-12 medium containing 10 % FBS was placed in the lower chamber. After incubation for 12 h, cells that have not invaded or migrated were gently wiped off from the upper chamber with a cotton swab, while cells in the lower chamber were stained with hematoxylin for 15 min. Number of invaded or migrated cells were determined in six fields, and the results were analyzed in triplicate.

Clonogenic assay

The MSCs-GC cells were inoculated into 6-well plates (2×10^3 cells/well) and kept at 37 °C in 5 % CO_2 for two weeks. Thereafter, co-cultured cells were fixed with 4 % paraformaldehyde, followed by staining with 1 % crystal violet. Colonies were photographed and counted. Experiments were conducted in triplicates.

Western blotting

The RIPA lysis buffer was used to extract total proteins. After electrophoresing on 10 % SDS-PAGE, proteins were transferred onto PVDF membranes, which were blocked with 5 % non-fat milk. Then the membranes were incubated with antibodies against SMARCA5 (1:1000, ab183730), vimentin (1:1000, ab92547), snail (1:1000, ab216347), slug (1:500, ab27568), β-catenin (1:5000, ab32572), Axin (1:2000, ab109307), c-myc (1:1000, ab32072) and MMP-7 (1:1000, ab207299) at 4 °C overnight. The next day, membranes were incubated with horseradish peroxidase-conjugated goat anti-rabbit IgG antibodies (1:2000, ab205718) for 2 h. The primary and secondary antibodies were obtained from Abcam, USA. Bands were observed with an enhanced chemiluminescence kit (Millipore, USA), while GAPDH was used as an internal control.

Statistical analysis

The data were analyzed by SPSS 23.0 (IBM, Armonk, NY, USA) and expressed as mean ± standard deviation (SD). All experiments were performed in triplicates. One-way analysis of variance (ANOVA) was used for difference comparison between multiple groups, followed by Turkey's posthoc tests. A value of $p < 0.05$ was considered statistically significant.

RESULTS

SMARCA5 was highly expressed in MSCs-treated gastric cancer cells

The SMARCA5 expression was quantified by western blotting in GES-1 cells and GC cell lines (AGS and MKN45). As shown in Figure 1 a, SMARCA5 was highly expressed in AGS and MKN45 cells, but not in GES-1 cells ($p < 0.001$). Afterward, the expression of SMARCA5 was determined when MSCs were applied in AGS and MKN45 cells. The results from Figure 1 b revealed that SMARCA5 expression was significantly elevated after MSCs application compared to that in untreated AGS cells ($p < 0.01$) or MKN45 cells ($p < 0.001$). In summary, the expression of SMARCA5 was promoted after MSCs treatment in gastric cancer cells.

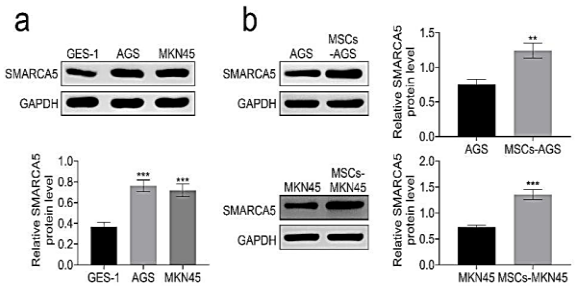

Figure 1: SMARCA5 expression was promoted after MSCs treatment with gastric cancer cells. (A): Western blotting depicted that SMARCA5 protein was highly expressed in AGS and MKN45 cell lines. ***$p < 0.001$, versus GES-1 cells. (B): Western blotting showing MSCs stimuli promoted SMARCA5 expression in AGS and MKN45 cells. **$P < 0.01$, versus AGS cells, ***$p < 0.001$, versus MKN45 cells

MSCs promoted the proliferation of gastric cancer cells

To evaluate the effects of MSCs on GC cell survival, cell viability was assessed in MSCs-treated AGS and MKN45 cells when si-SMARCA5 was transfected. Figure 2 a portrayed that MSCs dramatically increased cell viability compared to that of the untreated control group ($p < 0.001$), while si-SMARCA5 remarkably suppressed cell viability when compared with that of si-NC group ($p < 0.01$ or $p < 0.001$). Colony formation assays were subsequently conducted, and the results from Figure 2 b revealed that MSCs stimulation induced higher colony numbers compared to that of the untreated cells ($p < 0.001$), and si-SMARCA5 visibly decreased colony counts compared to that of si-NC group ($p < 0.001$). The results suggested that MSCs promoted GC cell proliferation, which was suppressed after the inhibition of SMARCA5.

MSCs facilitated gastric cancer cell invasion and migration

Moreover, Transwell assays were performed to evaluate cell invasion and migration in MSCs-treated GC cells after si-SMARCA5 transfection.

As presented in Figures 3 a and b, MSCs stimulation significantly provoked cell invasion in AGS and MKN45 cells when compared with those of untreated cells, whereas the transfection of si-SMARCA5 significantly decreased invasion cell numbers versus those of si-NC group (p < 0.001). Similar to the above results, MSCs-induced higher migration GC cells were obviously reduced by si-SMARCA5 compared with those of the si-NC group (p < 0.001). Taken together, the inhibition of SMARCA5 suppressed MSC-induced GC cell invasion and migration.

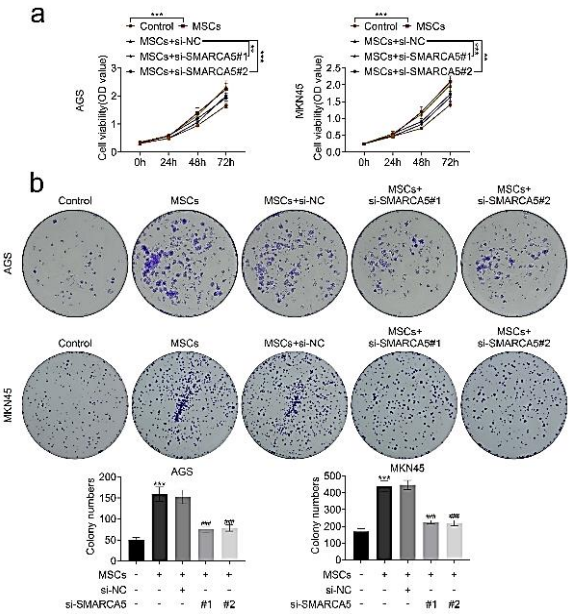

Figure 2: MSCs promoted the proliferation of gastric cancer cells by up-regulating SMARCA5. (A): CCK-8 assays identified MSCs increased gastric cancer cell viability, while inhibition of SMARCA5 suppressed cell viability. **P < 0.01, ***p < 0.001, versus control or si-NC group. (B): Colony formation assays revealed MSCs stimulation provoked colony formation, which was repressed by the inhibition of SMARCA5. ***P < 0.001, versus control group; $^{###}p$ < 0.001, versus si-NC group

MSCs triggered EMT of gastric cancer cells

To investigate whether MSCs were implicated in EMT of GC cells, the protein levels of vimentin, snail, and slug were quantified using immunoblotting (Figure 4). The results revealed that MSCs treatment elevated the levels of vimentin, snail, and slug in AGS and MKN45 cells when compared with those of untreated cells (p < 0.001), However, the inhibition of SMARCA5 significantly downregulated these proteins compared with that of the si-NC group (p < 0.05, p < 0.01 or p < 0.001). These findings suggest that MSCs promoted the EMT of GC cells, while this process was blocked by inhibition of SMARCA5.

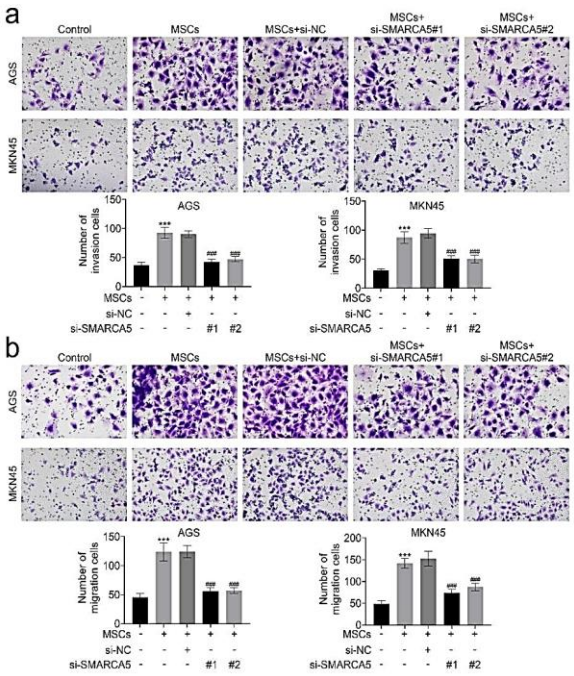

Figure 3: MSCs provoked gastric cancer cell invasion and migration through the up-regulation of SMARCA5. (A - B): Cell invasion and migration were evaluated using Transwell assays which showed that MSCs provoked cell invasion and migration, whereas si-SMARCA5 inhibited cell invasion and migration. ***p < 0.001, versus control group; $^{###}p$ < 0.001, versus si-NC group

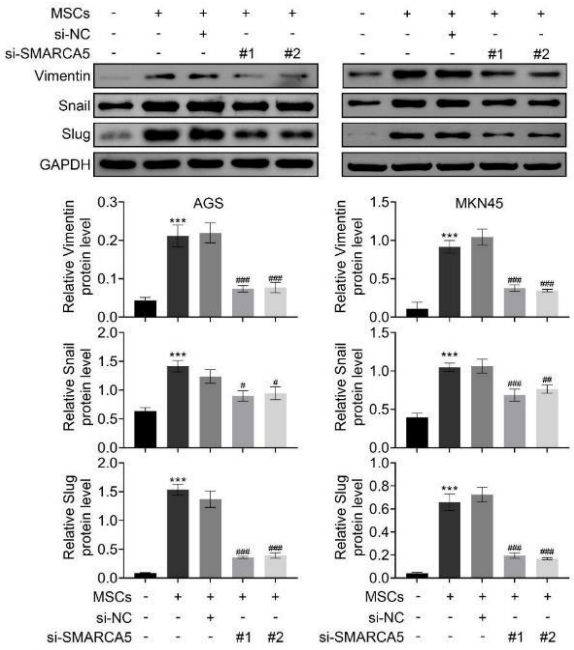

Figure 4: MSCs promoted EMT of gastric cancer cells by up-regulating SMARCA5. Immunoblotting showed that MSCs upregulated vimentin, snail, and slug in AGS and MKN45 cells, while the inhibition of SMARCA5 attenuated EMT. ***P < 0.001, versus control group; $^{#}p$ < 0.05, $^{##}p$ < 0.01 or $^{###}p$ < 0.001, versus si-NC group

MSCs enhanced oxaliplatin resistance in gastric cancer cells

As shown in Figure 5 a, the IC_{50} value was higher after MSCs treatment than in untreated cells ($p < 0.001$), whereas the knockdown of SMARCA5 decreased the value of IC_{50} ($p < 0.01$ or $p < 0.001$). Figure 5 b and c revealed that oxaliplatin significantly promoted cell apoptosis compared with cells without treatment ($p < 0.001$), while treatment of MSCs could mitigate oxaliplatin-induced apoptosis. However, the knockdown of SMARCA5 significantly reversed the effect ($p < 0.001$). The results suggest that MSc decreased the sensitivity of GC cells to oxaliplatin, while the knockdown of SMARCA5 increased the sensitivity of oxaliplatin.

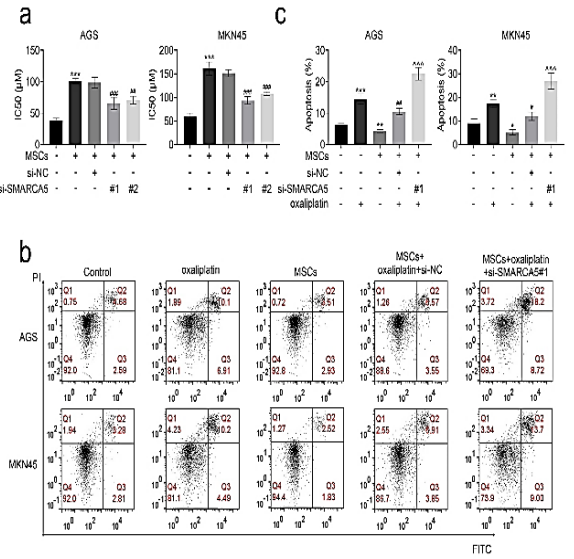

Figure 5: MSCs enhanced oxaliplatin resistance in gastric cancer cells through the up-regulation of SMARCA5. (A): Cell viability was assessed using the CCK-8 assay kit, and the IC_{50} value was calculated after oxaliplatin, MSCs, and si-SMARCA5 treatment. $^{***}P < 0.001$, versus untreated cells; $^{\#\#}p < 0.01$ or $^{\#\#\#}p < 0.001$, versus si-NC group. (B – C): Cell apoptosis was measured using flow cytometry following oxaliplatin, MSCs, and si-SMARCA5 treatment. $^{**}P < 0.01$, $^{***}p < 0.001$, versus untreated cells; $^{\#\#}p < 0.01$, versus oxaliplatin or MSC groups; $^{\wedge\wedge\wedge}p < 0.001$, versus si-NC group

MSCs activated Wnt/β-catenin signaling in gastric cancer cells

The protein expressions of β-catenin, Axin, c-myc, and MMP-7 related to Wnt / β-catenin signaling were measured to identify the role of MSCs in GC cells. Immunoblotting showed that the protein levels of β-catenin, c-myc, and MMP-7 were upregulated, but Axin was downregulated when exposed to MSCs in AGS and MKN45 cells versus those of the control group ($p < 0.001$). However, si-SMARCA5 transfection inhibited expressions of β-catenin, c-myc, and MMP-7 expression, while promoting Axin expression compared to that of the si-NC group ($p < 0.05$, $p < 0.01$ or $p < 0.001$) (Figure 6). MSCs activated Wnt/β-catenin signaling in GC cells, while the inhibition of SMARCA5 blocked this process.

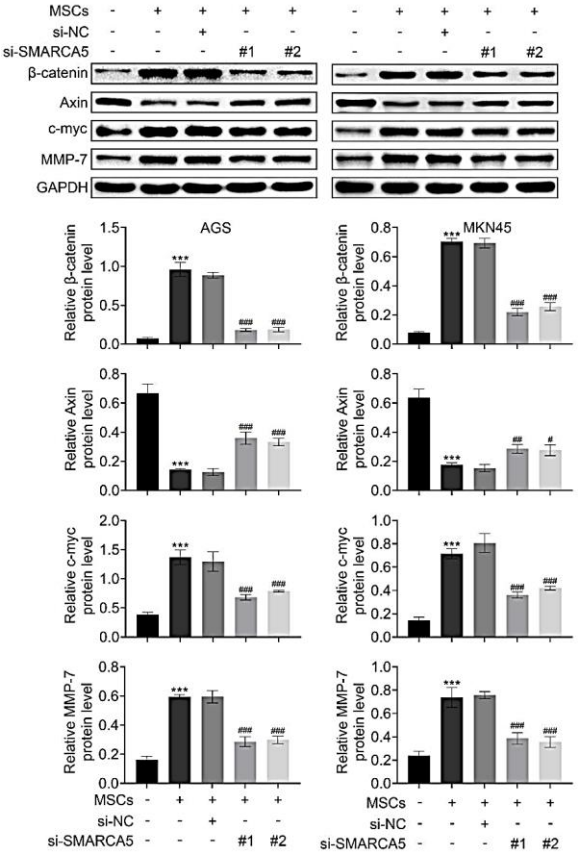

Figure 6: MSCs activated Wnt / β-catenin signaling in gastric cancer cells. Immunoblotting depicted MSCs upregulated β-catenin, c-myc, and MMP-7 but downregulated Axin in AGS and MKN45 cells, while inhibition of SMARCA5 inactivated Wnt/β-catenin. $^{***}P < 0.001$, versus control; $^{\#}p < 0.05$, $^{\#\#}p < 0.01$ or $^{\#\#\#}p < 0.001$, versus si-NC group

DISCUSSION

Cell invasion and migration are the key hallmarks of tumor metastasis. It has been proved that MSCs are associated with tumor growth and progression by participating in several crucial steps in tumor metastasis, such as promoting EMT and enhancing stem-like properties. As previously reported, the co-culturing of MSCs with breast cancer cells prompts directional migration through the regulation of transforming growth factor β (TGF-β1) [9]. Another study has demonstrated that MSCs in GC significantly promote the proliferation and migration of GC cells, rather than those in non-cancerous tissues, as well as the secretion of interleukin-8, leading

to GC cell progression [10]. MSCs were stimulated by the weekly metastatic breast tumor cells and subsequently secreted chemokine CCL5, which led to the enhancement of metastasis and invasion. In the present study, the results showed that MSCs co-cultured in AGS and MKN45 cells increased the expression of SMARCA5, and promoted cell proliferation, invasion, and migration, while the inhibition of SMARCA5 suppressed cancer cell proliferation, invasion, and migration, suggesting that MSCs enhanced GC progression, invasion, and migration.

In breast cancer, interferon-c (IFN-c) and/or tumor necrosis factor-a (TNF-a) provoked EMT in MSCs derived from adipose tissues by inhibiting E-Cadherin while enhancing vimentin expression, which lead to cancer cell invasion and migration. However, the silencing of the TGF-β1 receptor blocked EMT and motilities. It has been reported that GC tumor invades and migrates across endothelial cells through paracrine outputs after enhancement of EMT, which is mediated by increased β-catenin, MMP-16, snail, and twist expression [11]. Co-culturing of MSCs with A549 cells exhibited downregulated E-cadherin expression. Increased vimentin and snail, accompanied by the activation of autophagy and EMT, enhanced invasion and migration of GC cells. However, suppression of autophagy disabled MSCs-induced EMT and motilities. Additionally, co-culturing of MSCs and hepatocellular cancer cells presented significantly decreased E-cadherin expression, and increased levels of vimentin and slug, which suggested that MSCs enhanced cell metastasis via inducing EMT [12]. Moreover, cell fusion is considered to be essential in carcinogenesis, and a study has demonstrated that the hybrids between MSCs and gastric epithelial cells induced increased levels of N-cadherin and vimentin, as well as slug and twist. These findings imply that cell fusion between MSCs and gastric epithelial cells promoted invasion and migration by inducing EMT. This study revealed that MSCs significantly elevated the levels of vimentin, snail, and slug in AGS and MKN45 cells, whereas the inhibition of SMARCA5 significantly attenuated EMT.

Activated canonical Wnt signaling was confirmed to be implicated in the induction of EMT, resulting in the invasion [13]. Besides, the abnormal Wnt / β-catenin pathway promotes β-catenin accumulation in the cytoplasm, enhances β-catenin nucleus translocation, and increases cyclin D1, c-myc, and MMP-7. A recent study demonstrated that Steroid sulfatase (STS) enhanced the expression of cyclin D1, c-myc, and MMP-7, whereas, the inhibition of STS reversed this effect of β-catenin, cyclin D1, c-myc, and MMP-7 [14]. In addition, the highly expressed β-catenin and MMP-16 were involved in invasion and distant metastasis in intestinal-type GC. Axin is a concentration-limiting regulator, which accounts for the β-catenin destruction complex, and activated Wnt signaling induces Axin degradation. In this current study, the immunoblotting revealed that β-catenin, c-myc, and MMP-7 were upregulated but Axin was downregulated when exposed to MSCs in AGS and MKN45 cells, suggesting that MSCs activated Wnt / β-catenin signaling. However, si-SMARCA5 inhibited Wnt / β-catenin signaling in gastric cancer cells.

Mesenchymal stem/stromal cells (MSCs) are one of the key stromal cells in the tumor microenvironment, and their interaction with cancer cells leads to the transformation of naïve MSCs into tumour-associated MSCs. It has been recognized that cancer-associated MSCs induce tumor immune exclusion and resistance to immunotherapy. He and colleagues revealed that MSC-regulated lncRNA MACC1-AS1 promoted stemness and resistance to chemotherapy by inducing fatty acid oxidation in GC [15]. Compelling evidence has demonstrated that the mechanisms of cisplatin resistance were regulated by circular RNAs (circRNAs), which regulated tumor growth, chemosensitivity, and other biological behaviors in the tumor microenvironment. CircRNA SMARCA5 is considered as a tumor suppressor, while the overexpression of SMARCA5 is associated with cell proliferation, migration, and chemotherapy sensitivity [16]. In this study, MSCs facilitated GC cell invasion and migration through the up-regulation of SMARCA5. In addition, MSCs also promoted resistance to oxaliplatin through the up-regulation of SMARCA5.

A previous study has revealed that elevated levels of SMARCA5 which was a target of miR-146b-5p are observed in cell fusion between MSCs and glioma stem-like cells, and in turn, miR-146b-5p blocked cell proliferation and motilities by inhibiting SMARCA5 and inactivating the TGF-β pathway [17]. High expression of long non-coding RNA HAGLROS contributed to the malignancy of NSCLC by inhibiting miR-100 expression and subsequently increasing SMARCA5, while the inhibition of SMARCA5 reversed the effects [18]. As depicted in this study, the overexpression of SMARCA5 was observed in GC cells or enhanced after MSCs treatment, suggesting that highly expressed SMARCA5 might be implicated in GC progression. Conversely, the inhibition of

SMARCA5 suppressed GC cell proliferation, attenuated motilities, and inactivated the Wnt / β-catenin pathway.

CONCLUSION

This study demonstrates that MSCs facilitate GC cell growth and oxaliplatin resistance by upregulating SMARCA5 and activating Wnt/β-catenin signaling, thereby providing a potential strategy for GC treatment.

DECLARATIONS

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Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Yongli Nie and Jun Guo designed the experiments and carried them out. Jun Chen analyzed and interpreted the data, Yan yan Wang prepared the manuscript with contributions from all co-authors.

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