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Original Article

Safflower Polysaccharide Promotes Apoptosis and Inflammatory Response in Gastric Cancer Cells by Up-Regulating miR-6738-3p

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ABSTRACT

Objectives: To probe the action and mechanism of Safflower Polysaccharide (SPS) on Gastric Cancer (GC) cells. **Materials and Methods:** qRT-PCR detected miR-6738-3p expression levels. MTT assay and flow cytometry were adopted for the measurement of GC cell survival rate and apoptosis. ELISA analysis examined the levels of inflammatory factors. **Results:** miR-6738-3p was significantly decreased in GC cell lines, especially in AGS cells, relative to GES-1 cells. SPS treatment dose-dependently reduced the survival rate of AGS cells and induced cell apoptosis and inhibited inflammation. MiR-6738-3p overexpression also induced apoptosis enhancement and inflammation arrest in AGS cells. SPS increased miR-6738-3p content in AGS cells. Moreover, miR-6738-3p deletion reversed the functions mediated by SPS on AGS cell apoptosis promotion and inflammation suppression. **Conclusion:** Safflower polysaccharide promotes apoptosis and suppresses inflammatory reaction in GC cells by up-regulating miR-6738-3p.

Keywords: Apoptosis, Gastric Cancer, Inflammatory Factor, Mir-6738-3p, Safflower Polysaccharide, Sps.

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INTRODUCTION

Gastric Cancer (GC) accounts for the majority of cancer-related death through the world.[1,2] Helicobacter pylori infection and poor diet are the main risk factors for GC.[3] The surgery, chemotherapy and targeted therapy are still the main methods for GC treatment of gastric cancer.[4] However, long-term survival of GC patients remains unsatisfactory and most patients with GC will have recurrence and metastasis after radical gastrectomy.[5,6] GC seriously threatens human life and health all over the world, thus, it is urgent to find effective early diagnostic markers and therapeutic targets for GC patients.

Currently, Chinese herbs have been discovered to possess anti-cancer property.[7] Safflower is a plant in the Asteraceae/Compositae family possessing the effect of relieving pain, activating blood circulation and dispersing blood stasis.[8] Polysaccharide is one of the most important active components

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of safflower.[9,10] Safflower Polysaccharides (SPS) are identified to have antioxidant activity, immune regulation and anticancer effect.[10] In cancer, Luo *et al.* manifested that the metastasis and proliferation of breast cancer cells were suppressed by SPS.[11] SPS suppressed cell proliferation and evoked apoptosis by triggering M1 macrophage transition in colorectal cancer.[12] However, the action of SPS in GC remains vague.

Herein, this study analyzed the functions of SPS on the inflammatory response and apoptosis in GC cells and explored its potential molecular mechanism.

MATERIALS AND METHODS

Materials

Human normal gastric mucosal cells GES-1 and GC cell lines (AGS, HGC-27, N87 and SNU-484) were provided by the Procell (Wuhan, China); The Hyclone (USA) provided 10% FBS and DMEM; Trypsin, MTT assay kit and penicillin-streptomycin were purchased from Sigma (USA); Takara (Japan) provided Trizol reagent, reverse transcription kit and qRT-PCR kit; The bicinchonic acid (BCA) reagent kit and Annexin V-FITC/PI kit were provided by Shanghai Zeye; Beijing Solarbio provided the RIPA lysis buffer; The bicinchonic acid (BCA) reagent kit provided ELISA kits; MiR-NC, miR-6738-3p, anti-miR-NC, anti-miR-6738-3p were generated by Shanghai Genepharma; Lipofectamine2000 was provided by Invitrogen (USA). Primary Bcl-2, Bax and GAPDH antibodies, as well as HRP- labelled secondary antibody were obtained from Abcam (UK).

qRT-PCR

Extraction of total RNA was performed and then reversely transcribed into cDNAs, followed by qRT-PCR. The levels of miR-6738-3p were calculated by $2^{-\triangle\triangle Ct}$ method normalizing to U6.

MTT assay

AGS cells were maintained in DMEM plus penicillin-streptomycin and 10% FBS with 5% CO2 at 37°C. AGS cells at logarithmic stage were placed onto a 96 well plate (2.5×104 cells/mL) and incubated for 12 hr. Then each well was added with 0.16, 0.32, 0.64 and 1.28 mg/mL of SPS for 48 hr incubation. Thereafter, 20 μL MTT solutions were added in per well and 150 μL DMSO was used at for 5 min incubation at 37°C after 4 hr of cultivation. Lastly, the OD value at 490 nm was analyzed.

Cell transfection and treatment

AGS cells treated for 48 hr with 0.64 mg/mL SPS was named SPS group. Untreated cells were the Control group; AGS cells were transfected with miR-NC or miR-6738-3p for 48 hr, named miR-NC or miR-6738-3p group; anti-miR-NC or anti-miR-6738-3p was introduced into AGS cells, which were then exposed to 0.64 mg/mL SPS for 48 hr, named SPS+ anti-miR-NC or SPS+anti-miR-6738-3p group.

Flow cytometry

After indicated treatment, AGS cells were collected, rinsed with PBS and centrifuged. Then AGS cells were dyed with 10 μL Annexin V-FITC and 5 μL propidium iodide in binding buffer at 37°C for 15 min avoiding light, cell apoptosis was examined using flow cytometry.

Western blot

Extract total proteins from each cell group and quantify protein concentration using the BCA assay kit. About 60 μg protein underwent gel electrophoresis and then transferred to the PVDF membranes, followed by sealing with 5% skimmed milk. The primary antibodies at a dilution of 1:2000 was adopted to incubate for 12 hr at 4°C with the membranes, followed by HRP-labelled secondary antibody for 2 hr at 37°C. The images were exposed and developed in a dark room.

ELISA

The supernatant of each cell group was collected by centrifugation, the levels of IL-1β, IL-6 and TNF-α were examined as per the protocol of ELISA kits.

Statistical analysis

The data in line with normal distribution were expressed as (x±s) . Student *t* test or analysis of variance was utilized for statistical comparison. $p<0.05$ was considered statistically significant.

RESULTS

The decreased miR-6738-3p content in GC cells

As displayed in Table 1, miR-6738-3p levels were much lower in AGS, HGC-27, N87 and SNU-484 than those in GES-1 cells ($p<0.05$).

Table 1: miR-6738-3p content in GC cells. (x±s, *n*=9)

Group	miR-6738-3p
GES-1	1.00±0.08
AGS	0.47±0.03*
HGC-27	0.56±0.05*
N87	0.52±0.03*
SNU-484	0.63±0.04*
Effect size	2.367
F	164.012
p	0.000

Note: vs. GES-1, *$p<0.05$.

SPS reduces the survival rate of AGS cells

As exhibited in Table 2, the survival rate of AGS cells in 0.16, 0.32, 0.64, or 1.28 mg/mL SPS group was markedly quelled (p<0.05). 0.64 SPS was selected for subsequent analyses.

SPS treatment induces apoptosis and represses inflammation in AGS cells

The apoptosis of AGS cells was notably enhanced after SPS treatment, accompanied by the decreased Bcl-2 protein and increased Bax protein (Figure 1 and Table 3) (p<0.05). IL-1β, IL-6 and TNF-α content were discovered to be declined by SPS treatment (Table 3) (p<0.05).

SPS promotes miR-6738-3p expression in AGS cells

Levels of miR-6738-3p was increased by SPS treatment in AGS cells (Table 4) (p<0.05).

Overexpression of miR-6738-3p triggers apoptosis and impedes inflammation in AGS cells

The introduction of miR-6738-3p relative to miR-NC transfection markedly elevated miR-6738-3p, induced cell apoptosis, decreased Bcl-2 protein and elevated Bax protein, as well as repressed IL-1β, IL-6 and TNF-α contents (Figure 2 and Table 5) (p<0.05).

MiR-6738-3p deficiency reverses the functions of SPS on AGS cell apoptosis and inflammation

Relative to SPS+anti-miR-NC group, AGS cells in SPS+anti-miR-6738-3p group showed decreased apoptosis rate and Bax level, increased Bcl-2 levels, as well as elevated IL-1β, IL-6 and TNF-α levels (Figure 3 and Table 6) (P<0.05).

Table 2: Effects of different doses of SPS on the survival rate of AGS cells. (x±s, *n*=9)

Group	Survival rate (%)
Control	100.00±6.85
0.16 mg/mL	81.75±5.16*
0.32 mg/mL	73.18±6.23*
0.64 mg/mL	54.37±3.51*
1.28 mg/mL	43.24±2.76*
Effect size	2.925
F	170.689
p	0.000

Note: vs. Control group, *p<0.05

Table 3: SPS treatment induces apoptosis and represses inflammation in AGS cells. (x±s, *n*=9)

Group	Apoptosis rate (%)	Bcl-2	Bax	IL-1β (pg/mL)	IL-6 (pg/mL)	TNF-α (pg/mL)
Control	6.53±0.75	0.59±0.05	0.23±0.03	23.58±3.21	39.83±2.58	56.29±4.26
SPS	18.34±2.15*	0.19±0.02*	0.67±0.06*	12.16±1.18*	17.23±2.32*	32.35±1.67*
Effect size	7.335	10.505	0.420	4.723	9.212	7.399
t	15.560	22.283	19.677	10.018	19.541	15.696
p	0.000	0.000	0.000	0.000	0.000	0.000

Note: Same as Table 2, *p<0.05

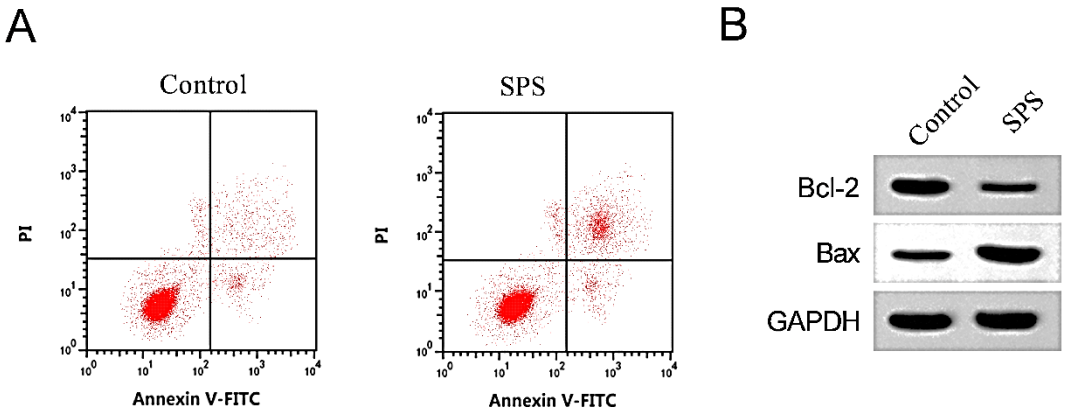

Figure 1: The effects of SPS on AGS cell apoptosis. A: Flow cytometry; B: Expression of apoptosis-related proteins.

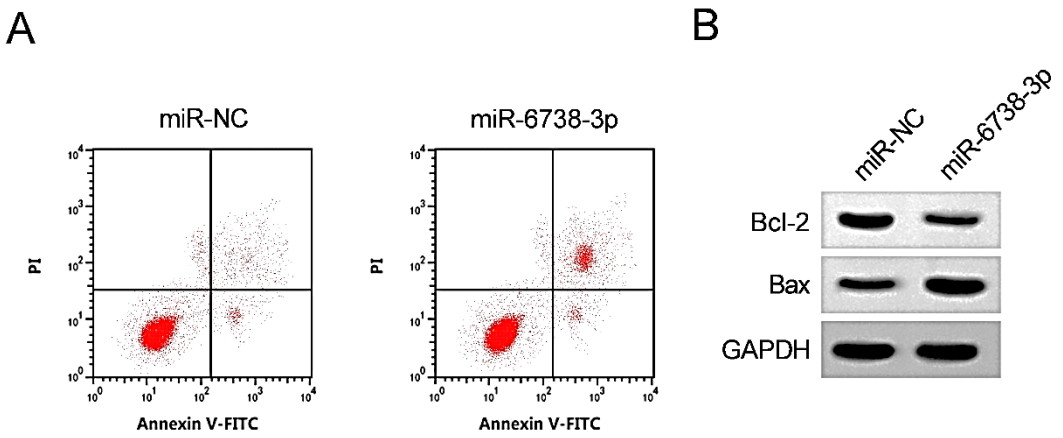

Figure 2: Functions of miR-6738-3p on AGS cells apoptosis and inflammation. A: Flow cytometry; B: Examination of Bax and Bcl-2 protein.

DISCUSSION

Numerous studies have shown that Chinese herbal extracts, such as shikosin, curcumin, baicalein and quercetin, have significant anticancer activity with low side effects. Moreover, previous researches have reported that SPS has anti-tumor and immunomodulatory functions. For instance, SPS impeded the growth of tongue squamous cell carcinoma by repressing the survival and cell cycle progression.[13] SPS hampered NSCLC cell growth by activating PI3K/Akt pathway and affecting immunomodulatory activities.[14] Shi *et al.* also suggested that SPS restrained lung cancer growth by enhancing the cytotoxicity of NK and CTL cells.[15] Herein, we probed the action of SPS on GC cell growth and inflammatory reaction. We found that SPS treatment markedly suppressed the survival of GC cells. Moreover, SPS triggered apoptosis, moreover, SPS led to an inhibition of inflammatory response. Thus, SPS showed anticancer effects on GC by suppressing HC cell growth and inflammation.

More and more evidence show that Chinese herbal extracts can play an anti-gastric cancer role by modulating the expression of miRNAs. For example, curcumin suppressed GC growth in nude mice and retarded cancer cell proliferative, invasive and migratory activities *in vitro* by up-regulating miR-194-5p via circ_0056618.[16] Luteolin restrained GC cell growth by increasing miR-34a expression level.[17] Formononetin repressed GC cell survival and mobility via modulating miR-542-5p content.[18] Gambogic Acid suppressed the mobility and viability of GC cells by miR-33a-5p.[19] Solasonine conferred chemotherapy sensitivity in GC cells and induced an inhibition of cancer cell proliferation.[20] Allicin impeded the metastasis and growth of GC by blocking ERBB4 via increasing miR-383-5p.[21] Epigallocatechin gallate enhanced GC cell death by down-regulating miR-29b.[22] Thus, the downstream miRNAs of SPS in GC cells were explored. We discovered that SPS markedly elevated miR-6738-3p content in GC cells. Previous research identified that low miR-6738-3p expression was tightly linked with advanced GC.[23] Whereas, the action of miR-6738-3p in GC and whether the anti-gastric cancer activity of SPS is related to miR-6738-3p remain unknown. Herein, we demonstrated that miR-6738-3p overexpression could induce apoptosis and suppress inflammation in GC cells. Importantly, the up-regulation of miR-6738-3p are able to abolish the anticancer action of SPS by repressing apoptosis and evoking inflammatory reaction in GC cells.

Table 4: SPS promotes miR-6738-3p expression in AGS cells. (x±s, *n*=9)

Group	miR-6738-3p
Control	1.00±0.05
SPS	1.92±0.14*
Effect size	8.752
t	18.566
p	0.000

Note; same as Table 2, *$p<0.05$.

miRNAs can target mRNAs by complementary base pairing between them, further leading to decreased translation, deadenylation and degradation of the mRNAs.[24] Thus, the proposed mechanism by which SPS induces apoptosis and inhibits inflammation in GC cells by elevating miR-6738-3p levels involves the modulation of specific genes of miR-6738-3p critical to cell survival and inflammatory processes. It is postulated that SPS may exert its effects by downregulating oncogenes that foster cell proliferation and survival, or by inhibiting the expression of genes that mediate inflammatory responses. This, in turn, could lead to a reduction in the secretion of pro-inflammatory cytokines. However, this hypothesis requires further experimental validation. To elucidate the exact mechanisms through which SPS operates, it will be necessary to identify the specific molecular targets of miR-6738-3p within GC cells. Understanding these targets will provide insights into the precise manner in which

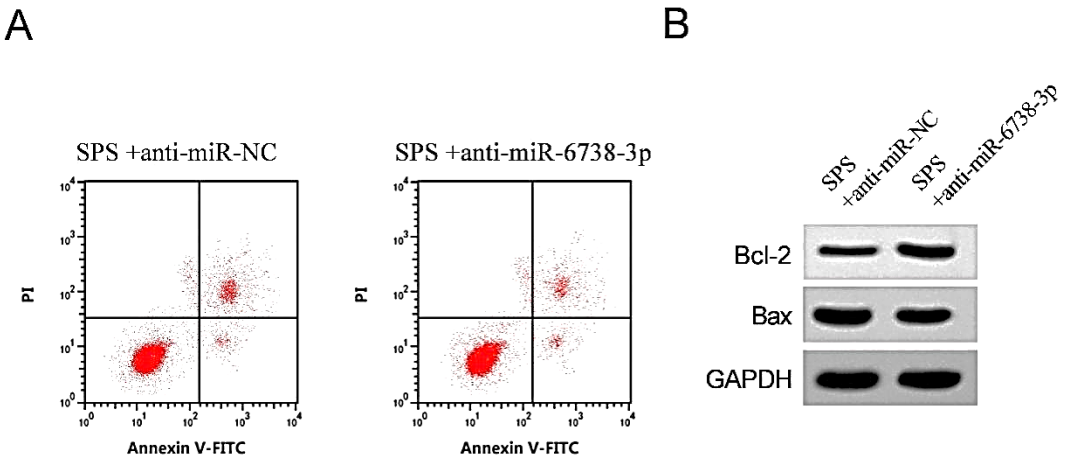

Figure 3: Functions of miR-6738-3p decrease on SPS-induced apoptosis of AGS cells. A: Flow cytometry; B: Expression of apoptosis-related proteins.

Table 5: miR-6738-3p rise triggers apoptosis and impedes inflammation in AGS cells.(x±s,n=9)

Group	miR-6738-3p	Apoptosis rate (%)	Bcl-2 protein	Bax protein	IL-1β (pg/mL)	IL-6 (pg/mL)	TNF-α (pg/mL)
miR-NC	1.01±0.07	7.15±0.53	0.56±0.04	0.25±0.02	26.14±2.25	42.67±3.34	53.11±3.26
miR-6738-3p	2.11±0.12*	21.47±2.89*	0.18±0.01*	0.71±0.08*	10.53±0.83*	16.36±1.12*	26.34±1.83*
Effect size	11.798	6.893	13.034	7.889	9.205	10.562	10.127
t	23.754	14.621	27.649	16.735	19.527	22.406	21.482
p	0.000	0.000	0.000	0.000	0.000	0.000	0.000

Note: vs. miR-NC group, *$p<0.05$.

Table 6: MiR-6738-3p deletion abates the functions of SPS on AGS cell apoptosis and inflammation. (x±s, *n*=9)

Group	miR-6738-3p	Apoptosis rate (%)	Bcl-2 protein	Bax protein	IL-1β (pg/mL)	IL-6 (pg/mL)	TNF-α (pg/mL)
SPS + anti-miR-NC	1.01±0.07	19.27±2.23	0.21±0.02	0.71±0.06	12.45±1.46	15.86±1.59	29.42±2.65
SPS+anti-miR-6738-3p	0.56±0.04*	12.15±1.37*	0.39±0.04*	0.47±0.03*	18.69±1.95*	31.53±2.36*	45.17±4.25*
Effect size d	7.894	3.847	5.692	5.060	3.623	7.788	4.447
t	16.745	8.161	12.075	10.733	7.685	16.520	9.434
p	0.000	0.000	0.000	0.000	0.000	0.000	0.000

SPS exercises its therapeutic influence. Moreover, to bridge the gap between laboratory research and clinical application, it is imperative to conduct clinical trials. These trials will be designed to evaluate the safety and efficacy of SPS in human patients, thereby translating the promising laboratory findings into tangible treatments that can be utilized in clinical practice.

In conclusion, SPS promoted apoptosis and suppressed inflammatory response in GC cells by up-regulating miR-6738-3p, laying a foundation for further revealing the anticancer effect of SPS on GC and enriching the regulatory relationship between Chinese herbal extracts and miRNA, which may contribute to our understanding of the pathological mechanism of GC and providing new ideas for SPS in the therapy of gastric cancer.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

SPS: Safflower Polysaccharide; **GC:** Gastric cancer; **BCA:** Bicinchonic acid.

SUMMARY

In Summary, SPS promoted apoptosis and suppressed inflammatory response in GC cells by up-regulating miR-6738-3p, laying a foundation for further revealing the anticancer effect of SPS on GC and enriching the regulatory relationship between Chinese herbal extracts and miRNA, which may contribute to our understanding of the pathological mechanism of GC and providing new ideas for SPS in the therapy of gastric cancer.

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