Original Article

MiRNA-130a-3p inhibits cell proliferation, migration, and TMZ resistance in glioblastoma by targeting Sp1

Zhijun Wang, Zhaohui Li, Yao Fu, Liang Han, Yu Tian

Departments of 1Neurosurgery, 2Pathology, China-Japan Union Hospital of Jilin University, Changchun 130033, P. R. China; 3Department of Pediatric Surgery, The First Hospital of Jilin University, Changchun 130000, P. R. China

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Abstract: Specificity protein 1 (Sp1) is aberrantly expressed and involved in the development and metastasis of glioblastoma. In this study, we observed that the expression of Sp1 was upregulated while that of microRNA (miR)-130a-3p was downregulated in glioblastoma cell lines. Sp1 was validated as a target of miR-130a-3p; increased levels of miR-130a-3p inhibited the proliferation, migration, and temozolomide (TMZ) resistance of the glioblastoma cells. However, Sp1 overexpression compromised the inhibitory effects of miR-130a-3p. Our study elucidates the functional interaction between miR-130a-3p and Sp1 in the development and progression of glioblastoma, suggesting a potential therapeutic target for the disease.

Keywords: Specificity protein 1, glioblastoma, miR-130a-3p, TMZ resistance, proliferation

Introduction

Glioblastoma (GBM) is the most malignant form of gliomas, with one of the highest mortality rates among cancers [1]. Owing to the infiltrative growth, angiogenesis, and apoptosis evasion, the 5-year survival rate of GBM patients is about 5% [2, 3]. Although major advancements have been made in surgery, chemoradiotherapy, gene therapy, and immunotherapy of GBM, poor prognosis and acquired resistance to chemotherapeutic agents result in treatment failure [4-6]. Thus, it is important to investigate the pathogenesis of GBM, identifying the potential targets that play key roles in the development and acquisition of drug resistance in GBM, in order to develop novel therapeutic strategies and to improve the outcome for the patients with this fatal disease.

The specificity protein 1 (Sp1), which belongs to the Sp/Kruppel-like factor (KLF) family of transcription factors, binds to the GC-rich promoter element through three Cys2His2-type zinc-fingers [7]. It is ubiquitously expressed in many tissues and involved in several pathophysiological processes, such as cell cycle progression, angiogenesis, and cell migration by modulating the expression of its target genes [8, 9], thereby affecting tumor progression and metastasis [10, 11]. Sp1 was observed to be aberrantly expressed in several human cancer types, including gliomas [12-17]. The overexpression of Sp1 promotes proliferation and invasion of glioma cells by upregulating multiple important oncoproteins, such as Matrix metalloproteinases-2 (MMP-2) [17], midkine (MDK) [18], and ADAM metallopeptidase domain 17 (ADAM17) [19]. Moreover, the expression of Sp1 is reported to affect the outcome of glioma patients, suggesting that Sp1 expression might be an independent prognostic indicator of the glioma patient survival [17].

Recent studies have shown that post-transcriptional regulation plays an important role in cancer progression [20, 21]. MicroRNAs (miRNAs) have emerged as important post-transcriptional regulators that repress gene expression by binding at the 3'-UTR region of the target genes [22, 23]. Several miRNAs are involved in major GBM regulatory pathways, including proliferation, differentiation, apoptosis, migration, and invasion [24], and thus associated with patient survival and therapeutic treatment response. Using the online software program starBase
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v2.0 and TargetScan, we noted that Sp1 might be a target of miR-130a-3p. Moreover, miR-130a-3p has been identified as a prognostic biomarker for colorectal cancer [25], gastric cancer [26], and hepatocellular carcinoma [27]. Thus, we speculate that Sp1 promotes GBM progression by downregulating miR-130a-3p expression. In this study, we examined the roles of Sp1 and miR-130a-3p in regulating the proliferation, invasion, and TMZ resistance of GBM, and investigated the interaction between Sp1 and miR-130a-3p.

Materials and methods

Cell lines and animals

The human astrocyte cell line HA1800, and human glioblastoma cell lines A172, U251, and U87 were purchased from the Cell Resource Center of Shanghai Institute of Life Sciences and grown in Dulbecco’s modified Eagle’s medium (DMEM, Gibco BRL Co. Ltd., USA) supplemented with 10% fetal bovine serum (FBS, Gibco BRL Co. Ltd., USA). BALB/c nude mice (male, 5-week-old, 16-20 g) were purchased from Shanghai Slack Laboratory Animal Co. Ltd. (animal license number: SCXK (Shanghai) 2012-0002). All the experimental procedures were conducted in accordance with institutional guidelines for the care and use of laboratory animals of Zhejiang Chinese Medical University, Hangzhou, China.

Plasmid construction and transduction

miRNA mimic, inhibitor, and their negative controls were synthesized by Biomics Biotechnologies Co., Ltd, Nantong, China. The Sp1 expression plasmid was constructed by inserting Sp1 cDNA (HG12024-ANG, Sino Biological Inc.) with N terminal GFPSpark tag into the pCMV3 vector. The Sp1 fragment containing the putative binding sites for miR-130a-3p was synthesized, annealed, and inserted between the Not I and Xba I restriction sites of the pmirGLO luciferase reporter vector (Promega, Madison, WI, USA) downstream of the luciferase gene, to generate the recombinant vectors Sp1-pmirGLO-wt and Sp1-pmirGLO-mut. For the Sp1-pmirGLO-mut con-struct, 7 mismatches were introduced into the Sp1 sequence. All the oligonucleotides and plasmids were transfected into cells using Lipofectamine 2000 (Invitrogen, USA), following the manufacturer’s instructions.

RNA extraction and quantitative real-time PCR

Total RNA was extracted from the cultured cells using TRIzol reagent (Invitrogen, USA). The relative levels of Sp1 and miR-130a-3p were examined using SYBR green real-time quantitative reverse transcription-PCR (real-time PCR). The cDNA was synthesized by using HiFi-MMLV cDNA kit (BeijingComWin Biotech Co., Ltd., Beijing, China). The real-time PCR reactions were performed on a Step One plus Real-Time PCR system (Applied Biosystems, USA) using the UltraSYBR Mixture (Beijing ComWin Biotech Co., Ltd.). The primers for Sp1 were 5’-TGGTGCGGCAGATGTTGTG-3’ (forward) and 5’-GCTATTGTCAGAGGAGGT-3’ (reverse); and for β-actin were 5’-GGCCACACACTTCACAT-3’ (forward) and 5’-GGGCTGTAAGGCTGTTG-3’ (reverse). The RT primer for miR-130a-3p was 5’-GGTCGCTCTGCGGAGGTGCAGGGTCCGAGGTATTCGCACC-AGAGCCAACATGCC-3’, and the PCR primers were 5’-GGCACTTTGAAAGTAAAAG-3’ (forward) and 5’-GGTGCGGAGGTCCGAGG-3’ (reverse). The U6 primers were 5’-CTCGCTTCGGCAGCACA-3’ (forward) and 5’-AACGCTTCACGAATTTGCC-3’ (reverse). The fold-change in expression for each gene was calculated using the 2ΔΔCt method.

Western blotting

Western blotting assay was performed as previously described [28]. The membranes were probed with rabbit polyclonal antibodies against human Sp1 (1:1000, Proteintech, USA) or mouse monoclonal β-actin antibody (1:2000, Huabio, China) at 4°C overnight, followed by incubation with horseradish peroxidase (HRP)-conjugated IgG antibody (Huabio, China). The protein bands were detected by enhanced chemiluminescence (Advansta, Menlo Park, CA, USA).

MTT assay

To determine the changes in cell proliferation rates, the cells were seeded at a density of 2×10^3 cells/well in a 96-well plate and incubated for 24, 48, 72, and 96 h. MTT (5 mg/mL) was added to each well, followed by an incubation of 4 h. After the supernatants were removed, dimethyl sulfoxide (DMSO) was added to each well and the absorbance value was measured at 570 nm using a SpectraMaxM3
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Colony formation assay

Cells (5×10^2) were independently plated onto 96-well plates. After 10-14 days, visible colonies were fixed with 4% paraformaldehyde and stained with 0.1% crystal violet in 20% methanol for 15 min. The colonies were then counted under a microscope (Nikon Eclipse Ti-S, Japan).

Transwell assay

Transwell inserts (diameter, 6.5 mm) with a pore size of 8 μM (Costar, Corning, NY, USA) were placed into the wells of 24-well culture plates. A total of 1×10^4 cells were transferred into the top chambers in serum-free DMEM while DMEM containing 20% FBS was added to the lower chambers. After 24 h of incubation, the non-migrated cells were removed with cotton swabs, and the migrated cells were fixed with 4% paraformaldehyde, stained with Giemsa, and observed under an ECLIPSE Ti-S microscope (Nikon, Tokyo, Japan). The experiments were independently repeated three times.

Cell cycle analysis

The cells were harvested, washed twice with PBS, and fixed with 70% ice cold ethanol overnight at 4°C. The fixed cells were resuspended in PBS containing 25 mg/mL propidium iodide (Nanjing KeyGenBiotech Co., Ltd. China) and 10 mg/mL RNase, and incubated for 30 min in the dark before being analyzed by a Guava easyCyte 8 Flow Cytometer (EMDMillipore, USA).

Cell apoptosis analysis

Apoptosis was analyzed using the Annexin-V-FITC/PI dual staining assay. The cells were seeded in 6-well culture plates at a density of 1×10^5 cells/mL. After 24 h of incubation, the cells were washed twice with PBS and resuspended in 500 mL binding buffer, and subsequently stained with FITC-Annexin-V and PI (Nanjing KeyGenBiotech Co., Ltd. China). The stained cells were quantified using a Guava easyCyte 8 Flow Cytometer (EMDMillipore, USA).

Luciferase activity assay

For luciferase reporter assay, the A172 cells were co-transfected with miRNA and Sp1-pmirGLO-wt/Sp1-pmirGLO-mut using Lipofectamine 2000. The luciferase activity was assayed 48 h after transfection using a Dual-Luciferase Reporter Assay system (Beyotime Institute of Biotechnology, Haimen, China). The values were normalized to those obtained for miRNA negative control transfections. All the transfection experiments were performed in triplicates.

Nude mouse xenograft studies

Male BALB/c nude mice (n=6; 16-20 g each) were injected with 1×10^7 U251-mimic, U251-inhibitor, U251-pCMV3-Sp1 + mimic, or U251 cells into their dorsal flanks. The length and width of the tumor xenografts were measured every 3 days starting from the 10th day after inoculation. The tumor volume was calculated using the formula V=W^2×L×0.5. When the tumors reached a size of 500 mm^3, the mice were sacrificed, and the xenografts weighed and dissected.

Immunohistochemistry

The dissected tumors were fixed overnight in 4% paraformaldehyde, embedded in paraffin, and then sectioned at a width of 5 mm per section. The sections mounted on the glass slides were deparaffinized and rehydrated. Then the sections were incubated with antibodies against the proliferation marker Ki-67 (Calbiochem, Cambridge, MA) and Sp1 (proteintech, USA), followed by incubation with the secondary antibodies. After the cell nuclei were stained with hematoxylin, the images were captured using a microscope (XSP-C204, Chongqing Optical Instrument Co., Ltd.).

Statistical analysis

The data are represented as mean ± SD of triplicate experiments. The statistically significant values were compared by Student’s test for pairwise comparison and by ANOVA for multivariate analysis, and P<0.05 was considered to indicate statistically significant data.
Results

Upregulation of Sp1 and downregulation of miR-130a-3p in GBM cell lines

We validated the expression levels of Sp1 in a normal human astrocyte cell line (HA1800) and 3 GBM cell lines (U251, U87, and A172) by real-time PCR and western blot analysis. As shown in Figure 1A and 1B, the expression of Sp1 was significantly higher in the 3 GBM cell lines as compared with that in the HA1800 cells (P<0.01). However, miR-130a-3p expression was downregulated in the three GBM cell lines as compared with that in HA1800 (Figure 1C, P<0.01).

MiR-130a-3p targets Sp1 to regulate its expression in GBM cells

To determine whether miR-130a-3p can suppress Sp1 expression, miR-130a-3p mimic or inhibitor and the negative controls (NC) were transfected into the three GBM cell lines. As shown in Figure 2A, in all the three GBM cell lines transfected with miR-130a-3p mimic and the inhibitor, the expression of Sp1 was significantly downregulated and upregulated, respectively, with protein expression being consistent with the mRNA status (Figure 2B). Additionally, the immunohistochemical (IHC) staining results (Figure 4D) showed that the tumor xenografts of the miR-130a-3p mimic group expressed less Sp1 than the tumors in the control group, whereas the inhibitor group expressed more Sp1 than the control group.

Using the predicted miR-130a-3p target sequence in the 3’-UTR of Sp1 (Figure 2C), we constructed luciferase reporter vectors Sp1-pmirGLO-wt and Sp1-pmirGLO-mut. The subsequent luciferase reporter assay demonstrated that miR-130a-3p mimic decreased the activity of Sp1-pmirGLO-wt but not of Sp1-pmirGLO-mut in the A172 cells (Figure 2D). However, no obvious effect on the reporter activity was observed in the miR-130a-3p mimic NC groups. These results revealed that Sp1 is a target of miR-130a-3p, with miR-130a-3p regulating the mRNA and protein expression of Sp1 in the GBM cells.

MiR-130a-3p affects GBM cell proliferation in vitro and in vivo

We first evaluated the effect of miR-130a-3p on cellular proliferation using MTT assay and colony formation assays in the A172 and U251 cells. MTT assay showed that miR-130a-3p mimic- and inhibitor-transfected A172 cells exhibited significantly lower and higher growth rates than the control cells at 72 h after plating, respectively. The miR-130a-3p mimic-transfected U251 cells exhibited lower growth rate than the control cells 48 h after plating, whereas the miR-130a-3p inhibitor-transfected U251 cells exhibited higher growth rates both at 48 h
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and 72 h after plating (Figure 3A, *P<0.05, **P<0.01). The colony formation assay consistently showed that enforced expression of miR-130a-3p dramatically reduced the number of colonies in the two GBM cell lines after 14 days of culture as compared to that in the controls. In contrast, the number of colonies of miR-130a-3p inhibitor-transfected cells was significantly higher than that in the control cells (Figure 3B). Furthermore, we observed that miR-130a-3p mimic-transfected GBM cells had increased frequency of G0/G1 phase cells and decreased frequency of S and G2/M phase cells. Conversely, miR-130a-3p inhibitor-transfected GBM cells had reduced frequency of G0/G1 phase cells and increased frequency of S and G2/M phase cells (Figure 3C).

To confirm the effect of miR-130a-3p on tumor behavior in vivo, we subcutaneously implanted miR-130a-3p mimic or inhibitor-transduced U251 cells, respectively, into the flanks of BALB/c nude mice and monitored the tumor growth (Figure 4A). The growth curve of tumor xenografts and the histogram of tumor weight showed that high miR-130a-3p levels significantly slowed down the tumor growth, whereas low miR-130a-3p levels promoted tumor growth in vivo (Figure 4B and 4C). The IHC staining results showed that miR-130a-3p mimic-transfected cells in the GBM tumor xenografts displayed lower Ki67 expression while miR-130a-3p inhibitor-transfected cells displayed higher Ki67 expression, as compared with the control cells (Figure 4D). These findings indicated that the exogenous miR-130a-3p was able to inhibit GBM growth in vitro and in vivo.

**MiR-130a-3p affects migration and TMZ resistance of glioblastoma cells**

Next, we evaluated the effect of miR-130a-3p on the migration of GBM cells. The transwell assay showed that the migration of miR-130a-3p mimic-transfected GBM cells was markedly slower than that of the control cells, and the
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Figure 3. The effect of miR-130a-3p on the proliferation of glioblastoma cells. A. MTT assay was performed on A172 or U251 cells transfected with miR-130a-3p mimic or inhibitor. *P<0.05, **P<0.01 mimic group compared with control group; #P<0.05, ##P<0.01 inhibitor group compared with control group. B. Colony formation assay was performed in A172 and U251 cells after miR-130a-3p mimic or inhibitor transduction. The experiments were performed three times in triplicates, and the average scores are indicated with error bars on the histogram. C. The cell cycle distribution of A172 and U251 cells transfected with mimic or inhibitor was analyzed by flow cytometry.
Figure 4. The establishment of xenograft tumor model and IHC analysis of Ki67 and Sp1 expression in xenograft tumor tissues. (A-C) Tumor images (A), tumor volume, and tumor weight from mice. (D) IHC analysis of Ki67 and Sp1 expression in glioblastoma tumor xenografts. The intensities of Ki67-positive cells and Sp1-positive cells were calculated with Image J software (×400). *P<0.05, **P<0.01 mimic group compared with control group; #P<0.05, ##P<0.01 inhibitor group compared with control group. &P<0.05, &&P<0.01 mimic group compared with pCMV-Sp1 + mimic group.
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migration of miR-130a-3p inhibitor-transfected cells was much faster than that of the control cells (Figure 5A and 5B). Since temozolomide (TMZ) is one of the most commonly used drugs for the clinical treatment of GBM, we asked whether miR-130a-3p expression was associated with the TMZ resistance of the GBM cells. The control, miR-130a-3p mimic-, and inhibitor-transfected A172 or U251 cells were treated with TMZ (5-30 µg/mL). After 48 h, MTT assay was performed to examine the cell proliferation. As shown in Figure 6A, miR-130a-3p mimic significantly suppressed the proliferation of TMZ-treated A172 or U251 cells as compared with that in the control group. However, transfection with miR-130a-3p inhibitor caused an increase in the proliferation of A172 or U251 cells, as compared with that in the control group. These data indicate that miR-130a-3p treatment increased the TMZ-induced inhibition of GBM cell proliferation. It was further observed that miR-130a-3p mimic treatment also led to a significant increase in the apoptosis of TMZ-treated A172 or U251 cells, whereas miR-130a-3p inhibitor treatment reduced the apoptosis of TMZ-treated A172 or U251 cells, as compared to that in the control group (Figure 6B and 6C), indicating that miR-130a-3p treatment also promoted the TMZ-induced apoptosis of GBM cells.

Sp1 overexpression abrogates anti-proliferation and anti-migration effects of miR-130a-3p in glioblastoma cells

To assess the role of functional interactions between miR-130a-3p and Sp1 in cell prolifera-
tion and migration of the GBM cells, the miR-130a-3p mimic and pCMV3-Sp1 were co-transfected into the GBM cells. After 72 h of incubation, the cell proliferation was evaluated by MTT assay. The data showed elevated cell viability in miR-130a-3p mimic + pCMV3-Sp1-transfected cells as compared to that in the miR-130a-3p mimic + pCMV empty vector-transfected cells (Figure 7A). As shown in Figure 4D, the mean volume and weight of the tumors in the pCMV-Sp1 + mimic group was significantly higher than that in the mimic group, indicating that Sp1 overexpression abrogates the anti-proliferation effects of miR-130a-3p. Furthermore, the inhibition of cell migration by miR-130a-3p mimic treatment was also abrogated by Sp1 overexpression (Figure 7B).

Sp1 overexpression reduces the increased TMZ-sensitivity induced by miR-130a-3p mimic in glioblastoma cells

We next evaluated the effect of Sp1 overexpression on TMZ-sensitivity in the GBM cells in the presence of miR-130a-3p mimic. The MTT assay results showed that the increased TMZ-sensitivity induced by miR-130a-3p mimic treatment was reduced after Sp1 overexpression (Figure 8A). We then examined whether the overexpression of Sp1 could reduce the apoptosis of TMZ-treated cells induced by miR-130a-3p mimic treatment. As shown in Figure 8B and 8C, the cell apoptosis rate of miR-130a-3p mimic-transfected cells plus TMZ treatment was reduced by Sp1 overexpression as compared to that in the miR-130a-3p mimic-transfected cells.

Figure 5. The effect of miR-130a-3p on the migration of A172 (A) and U251 (B) cells. The cells were transfected with the miR-130a-3p mimic and inhibitor. The number of migrating cells was determined using transwell assay (without Matrigel) (magnification, ×200). **P<0.01.
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Figure 6. The effect of miR-130a-3p on the TMZ resistance of glioblastoma cells. A. MTT assay was performed on miR-130a-3p mimic and inhibitor-transfected A172 or U251 cells after treatment with TMZ (5-30 µg/ml) for 48 h. B. Annexin-V-FITC/PI dual staining assay was performed to evaluate the ratio of apoptotic cells in miR-130a-3p mimic and inhibitor-transfected A172 or U251 cells after treatment with TMZ. C. The histogram representing the number of apoptotic cells in miR-130a-3p mimic and inhibitor-transfected cells after treatment with TMZ. *P<0.05, **P<0.01.
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Discussion

In recent years, miR-130a-3p, a member of the miR-130 family and a key regulator of tumor progression and metastasis, has been gaining attention. Interestingly, some reports have shown that the miRNAs of the miR-130 family are upregulated and promote cell proliferation in several types of cancers [26, 29-31], while other studies concluded that miR-130 family members are downregulated and inhibit cell proliferation [27, 32-34], indicating the complexity of miR-130 function during tumorigenesis. In this study, we found miR-130a-3p to be significantly downregulated in A172, U251, and U87 GBM cell lines. The enforced expression of miR-130a-3p using miRNA mimics reduced the glioblastoma cell proliferation. Conversely, the knockdown of miR-130a-3p expression using miRNA inhibitors promoted the GBM cell proliferation. Moreover, the function of miR-130a-3p in cell proliferation in vivo was consistent with the in vitro status. The miR-130a-3p mimic significantly slowed the tumor growth and the miR-130a-3p inhibitor accelerated the tumor growth in a nude mouse xenograft tumor model. We also demonstrated that the miR-130a-3p mimic inhibited cell migration while the miR-130a-3p inhibitor increased the migration of glioblastoma cells in vitro.

The current standard therapy for GBM includes surgery, radiotherapy, and chemotherapy with the alkylating agent TMZ [35], with TMZ resistance often leading to GBM recurrence and poor outcomes [36, 37]. Therefore, we evaluated the effect of miR-130a-3p on TMZ resistance in the GBM cells. We found that miR-130a-3p mimic greatly increased the sensitivity of the GBM cells to TMZ, while the sensitivity...
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was decreased in the cells transfected with miR-130a-3p inhibitor, indicating that miR-130a-3p might be an important modulator of TMZ resistance in the GBM cells.

The elevated expression of Sp1 and its participation in cell proliferation, invasion, and chemoresistance has been demonstrated in gliomas [38-41]. Using bioinformatics analysis, we predicted that Sp1 was one of the targets of miR-130a-3p. This observation was supported by the reciprocal repression of miR-130a-3p and Sp1 in GBM cells. The addition of miR-130a-3p mimic inhibited the expression of Sp1 whereas miR-130a-3p inhibitor enhanced the Sp1 expression. Moreover, the luciferase activity assay confirmed that Sp1 is a direct and functional target of miR-130a-3p. The functional interaction between miR-130a-3p and Sp1 during the GBM cell proliferation, metastasis, and chemoresistance was further demonstrated by analyzing the cell viability, cell migration, and TMZ sensitivity. We propose that elevated Sp1, induced by decreased miR-130a-3p, may promote cell proliferation, migration, and TMZ resistance, and consequently facilitate the development and progression of GBM.

In conclusion, miR-130a-3p was found to reduce cell proliferation, migration, and TMZ resistance. The downregulation of miR-130a-3p in GBM induced the upregulation of its target gene Sp1, thereby promoting the malignant behavior and TMZ resistance of the GBM cells. The elucidation of the functional interactions between miR-130a-3p and Sp1 in the development and progression of GBM may provide a therapeutic target for the treatment of GBM.

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Disclosure of conflict of interest

None.

Address correspondence to: Liang Han, Department of Pathology, China-Japan Union Hospital of Jilin University, Xiantai Street 126, Changchun, P. R. China. Tel: +86-0431-89876953; Fax: +86-0431-89876953; E-mail: hzhrlju.edu.cn; Yu Tian, Department of Neurosurgery, China-Japan Union Hospital of Jilin University, Xiantai Street 126, Changchun, P. R. China. Tel: +86-0431-84995639; Fax: +86-0431-84995639; E-mail: tianyu@jlu.edu.cn

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