

# *XRCC1* rs1799782 (C194T) polymorphism correlated with tumor metastasis and molecular subtypes in breast cancer

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**Background:** Breast cancer, a malignant tumor with its highest incidence in women, affects physical and mental health, and can even be life-threatening. In recent years, its incidence has continued to grow, accompanied by a trend of younger onset. *XRCC1* is well known as a DNA-repair gene, and its abnormal expression is related to the occurrence of various malignant tumors.

**Methods:** In this study, we detected *XRCC1* expression and investigated its association with the *XRCC1* rs1799782 polymorphism. *XRCC1* was overexpressed to investigate its effect on in breast cancer cells. CCK8 and clone formation efficiency assay were used to detect cell proliferation. Transwell assay was performed to confirm cell migration and invasion. Flow cytometry was used to detect cell apoptosis.

**Results:** In 118 breast cancer samples, CC genotype frequency was 49.15% (58 of 118), CT genotype frequency was 42.37% (50 of 118), and TT genotype frequency was 8.48% (ten of 118). Lymphatic metastasis was associated with a higher frequency of *XRCC1* rs1799782 polymorphism ( $P < 0.05$ ), and breast cancer patients with positive PR, HER2, and negative ER had high *XRCC1* rs1799782 frequency ( $P < 0.05$ ). Meanwhile, *XRCC1* had low expression in breast cancer (74.6%, 88 of 118) and high expression in ER-negative, PR-negative, HER2-positive and Ki67-low-expression patients. *XRCC1* rs1799782 may play an important role in the development and metastasis of breast cancer. These results differ from previous studies that did not suggest that rs1799782 is effective in breast cancer. We also investigated the role of *XRCC1* in breast cancer progression.

**Conclusion:** We have proved that *XRCC1* can inhibit proliferation and invasion and promote apoptosis of breast cancer cells. *XRCC1* expression was regulated by the JNK pathway. We found that the JNK inhibitor SP600125 significantly inhibited the growth of breast cancer cells, and consider it a potential drug for breast cancer.

**Keywords:** MCF7, gene expression, proliferation, apoptosis, JNK pathway

## Introduction

Tumor occurrence and development is a complex multistage process that is related to molecular-level variation in many genes. *XRCC1* is well known as a DNA-repair gene, and its abnormal expression is related to the occurrence of various malignant tumors.<sup>1-3</sup> Single-nucleotide polymorphisms (SNPs) of *XRCC1* at multiple loci are closely related to tumor susceptibility and progression, including in lung cancer, breast cancer, bladder cancer, gastric cancer, skin cancer, colorectal cancer, prostate cancer, and head and neck cancer.<sup>4-7</sup> However, due to the interference of genetic and individual factors, there is still wide divergence in the relationship between SNPs of the DNA-repair gene *XRCC1* and tumor susceptibility. It is difficult to establish a clear correlation between *XRCC1* SNPs and the susceptibility of a specific tumor on the basis of existing studies. In addition,

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related research on *XRCC1* in tumors has been mostly focused on gene SNPs and tumor susceptibility, and specific roles and mechanisms in tumors have received less attention. Therefore, in this study, we not only explored SNPs and tumor susceptibility but also studied the specific function and mechanism of *XRCC1* in breast cancer. Studies have shown that the *XRCC1* rs1799782 (C194T) polymorphism may play an important role in the expression of *XRCC1*. Therefore, we focused on the relationship between this site and the pathological features of breast cancer in this study.

In our preceding studies, sequencing results of breast cancer samples showed a significant increase in the frequency of *XRCC1* rs1799782 polymorphism in breast cancer samples, the role of which was controversial in breast cancer.<sup>8</sup> In this study, we detected *XRCC1* expression and investigated associations with the *XRCC1* rs1799782 polymorphism to predict sensitivity to chemotherapy and prognosis, which has the potential to guide clinical diagnosis and treatment.

## Methods

### Agents and PCR primers

The genomic DNA-extraction and DNA-sequencing kits used in this research were purchased from Axygen (AP-96-BL-GDNA) and Beckman Coulter (Qiagen PyroMark PCR kit), respectively. SP600125 was obtained from the American MedChemExpress. PCR and sequencing primers were: *XRCC1* sense, 5'-ATGCCGTCCCAGGTAAGC-3'; antisense, 5'-AGCCCCAAGACCCGGTCACT-3'.

### Clinical specimens

A total of 118 breast cancer patients in Qianfoshan Hospital between March 2014 and December 2015 were selected. Patients were all female aged 31–88 years. The median age was 49 years. No patients received chemotherapy, endocrine therapy or radiotherapy before surgery, and all were confirmed to have aspecific invasive carcinoma. Peripheral blood (3–5 mL) was drawn from patients for genomic DNA extraction. All individuals supplied written informed consent to participate, and this was approved by the ethics committee of Shandong Provincial Qianfoshan Hospital.

### Immunohistochemistry

Immunohistochemistry was performed to detect the *XRCC1*-expression levels in breast cancer. Patient specimens were fixed in 10% paraformaldehyde in PBS for 12 hours and then embedded in paraffin wax. Paraffin-block-embedded normal and tumor breast-tissue samples were cut into 4  $\mu$ m sections. After dewaxing in xylene, sections were repaired in citrate buffer and blocked with 10% goat serum for 1 hour. *XRCC1*

(Abcam) antibody was added (1:100) to the sections, which were incubated in a humid chamber at room temperature for 1 hour. For the negative control, the *XRCC1* antibody was replaced with PBS. Tissue in which  $\leq 10\%$  of cancer cells were positively stained was recorded as 0.1 point, with 10%–49% as 0.5 point and  $\geq 50\%$  as 1 point. Based on staining intensity, groups were divided into those with 0, 1, 2, and 3 points. *XRCC1*-expression levels of samples were then categorized as low ( $< 1$  point) and high ( $\geq 1$  point). Results were analyzed independently by two pathologists.

### Cell culture and transfection

The breast cancer cell lines MCF7 and MDA-MB231 were purchased from the cell bank of the Chinese Academy of Sciences (Shanghai, China). Cells were cultured in RPMI 1640 medium with 10% FBS, 0.1 mg/mL streptomycin, and 100 U/mL penicillin. Cells were seeded on six-well plates. *XRCC1*-OV transfection was applied using Lipofectamine 2000 following the manual. Cells were treated with the JNK-specific inhibitor SP600125 (MCE, 10  $\mu$ M) for 8 hours for the next experiment.

### Quantitative fluorescence PCR

Total RNA was isolated from MCF7 cells using an UltraPure RNA-extraction kit with reverse transcription and fluorescence quantitative PCR performed using a HiFiScript cDNA-synthesis kit and UltraSYBR mixture kit, respectively. Primers were: *XRCC1* sense, 5'-CCCAGAAGGTGACAGTGACC-3'; antisense, 5'-AGACTGGAGAGGCTGAGGAG-3'; GAPDH sense, 5'-GATTTGGTCGTATTGGGCGC-3'; and antisense, 5'-TTCCC GTTCTCAGCCTTGAC-3'. mRNA-expression levels were calculated using the comparative CT method after normalization to GAPDH.

### Western blot

After transfection, cells were lysed with RIPA buffer containing 1.0% NP-40, 150 mM NaCl, 0.1% Triton X-100, 0.5% sodium deoxycholate, 0.1% SDS, 50 mM Tris-HCl pH 8.0, and protease inhibitors. Protein concentrations were detected using a BCA protein-assay kit. Protein samples were separated on 5%–10% SDS-PAGE gel. Membrane-contained target protein was incubated with primary antibodies at a dilution of 1:1,000. The primary antibodies *XRCC1* (Abcam), Bcl2 (Proteintech), caspase 3 (Proteintech), Bax (Proteintech), tubulin (Proteintech), p70 (Proteintech), JNK (Proteintech), pJNK (Proteintech), STAT3 (Abcam), and pSTAT3 (Abcam) were used in this study. Assays were repeated three times. Relative protein-expression levels were calculated by determining a ratio between the amount of target protein and GAPDH.

## Cell-proliferation assays

Cell vitality was detected every 24 hours after transfection by adding 10  $\mu$ L cell counting kit-8 (CCK8) reagent. Cells were incubated at 37°C for 90 minutes and then OD values detected using a microplate reader at 450 nm.

## Clone-formation-efficiency assays

Cells were collected and seeded in 10 cm plates at a density of 100 cells/mL medium. Cells were incubated at 37°C until formation of sufficiently large clones. After incubation for 7 days, cells were fixed with 4% paraformaldehyde and stained with 0.1% crystal violet. The number of colonies was calculated and compared with experimental negative controls.

## Cell-invasion and -migration assays

Transwell assays were performed to evaluate cell invasion and migration. Cells ( $10^4$ ) were seeded in 24-well invasion chambers and inserts coated with Matrigel. Transwell assay for migration had no Matrigel coating. After incubation for 24 hours, noninvading cells were removed using a cotton swab. Chambers were washed with PBS twice. Cells were stained with 0.1% crystal violet, and total numbers of cells were averaged from triplicate determinations.

## Cell-apoptosis analysis

Cells were incubated in serum-free medium for 24 hours and then resuspended in binding buffer (2.5 mM  $\text{CaCl}_2$ , 140 mM NaCl, 10 mM HEPES/NaOH pH 7.4) at an intensity of  $3\text{--}5 \times 10^5$  cells/mL. Annexin V–fluorescein isothiocyanate and propidium iodide were added to cell suspensions, incubated at room temperature in the dark, and analyzed with flow cytometry. Cell apoptosis was analyzed using BD FACSDiva software.

## Statistical analysis

All data were analyzed using SPSS 18 statistical software (SPSS, Chicago, IL, USA). Pearson  $\chi^2$  was performed to determine correlations between *XRCC1* levels/mutation rate and clinical parameters. An ANOVA test was performed to analyze the changes between each group in cell line experiment.  $P < 0.05$  were considered significant.

## Results

### *XRCC1* rs1799782 (C194T) polymorphism is correlated with molecular subtype and tumor metastasis in breast cancer

Sequencing of the 118 patient samples showed a higher frequency of *XRCC1* rs1799782 polymorphism in breast

**Table 1** *XRCC1* rs1799782-polymorphism distribution and association of molecular subtypes of breast cancer

	Cases	<i>XRCC1</i> rs1799782 (n)		P-value
		CC	CT/TT	
Luminal A	21	9	12	<0.05
Luminal B	56	37	19	
HER2-positive	32	6	16	
Triple-negative	19	6	13	

cancer. *XRCC1* (C194T) had three visible genotypes: CC, CT, and TT. In this study, CC frequency was 58.47% (69 of 118), CT 38.98% (46 of 118), and TT 2.54% (three of 118) in paracancerous tissues. However, in tumor tissue, CC frequency was 49.15% (58 of 118), CT 42.37% (50 of 118), and TT 8.48% (ten of 118). The sequencing results suggested a high frequency of *XRCC1* rs1799782 polymorphism in breast cancer. Genotype distributions of *XRCC1* rs1799782 were significantly different with molecular subtypes of breast cancer. *XRCC1* rs1799782 showed high frequency in luminal A, HER2-positive, and triple-negative breast cancer (Table 1). As shown in Table 2, there was no significant difference for age, tumor size, pathological grade, or *XRCC1* rs1799782 frequency ( $P > 0.05$ ). Lymphatic metastasis was

**Table 2** *XRCC1* rs1799782-polymorphism distribution and association of clinicopathological features of breast cancer

	Cases	<i>XRCC1</i> rs1799782 (n)		P-value
		CC	CT/TT	
<b>Age, years</b>				>0.05
$\geq 49$	71	35	36	
<49	47	23	24	
<b>Tumor size</b>				>0.05
$\geq 2$ cm	73	40	33	
<2 cm	45	18	27	
<b>Pathological grade</b>				>0.05
I	13	4	9	
II–III	105	54	51	
<b>Lymphatic metastasis</b>				<0.05
Positive	47	34	13	
Negative	71	24	47	
<b>ER</b>				<0.05
Positive	76	43	33	
Negative	42	15	27	
<b>PR</b>				<0.05
Positive	68	28	40	
Negative	50	30	20	
<b>HER2</b>				<0.05
Positive	37	9	28	
Negative	81	49	32	
<b>Ki67</b>				<0.05
High	87	37	50	
Low	31	21	10	



associated with a higher frequency of *XRCC1* rs1799782 polymorphism ( $P < 0.05$ ), and breast cancer patients with positive PR and HER2 and negative ER had high *XRCC1* rs1799782 frequency ( $P < 0.05$ ).

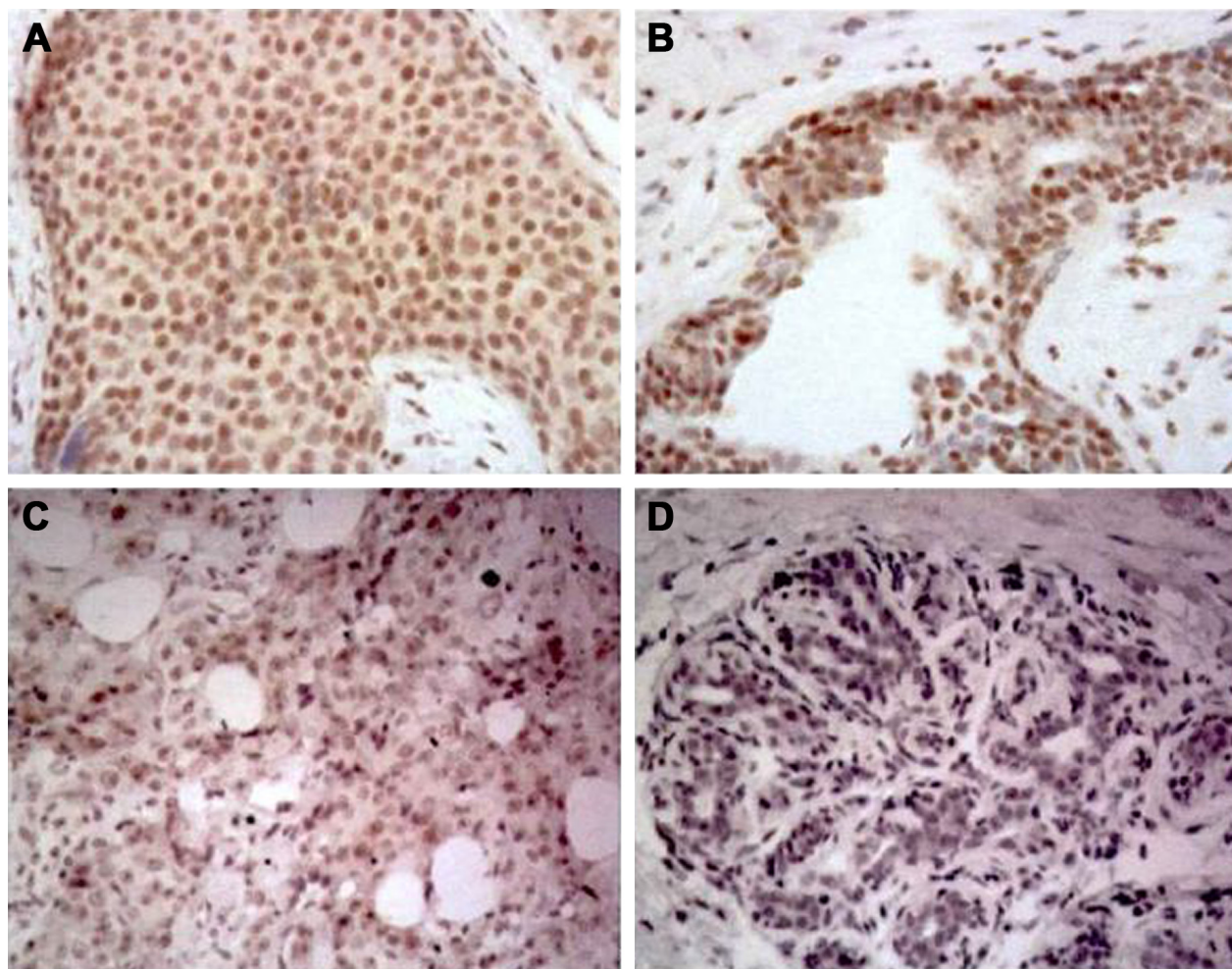
### *XRCC1* expression is correlated with tumor metastasis and molecular subtypes in breast cancer

Immunohistochemistry was performed to investigate further the expression level of *XRCC1* in breast cancer tissue. The results (Figure 1) showed that *XRCC1* expression was low in breast cancer (74.6%, 88 of 118). We next evaluated correlations between *XRCC1*-expression and clinicopathological variables in breast cancer patients. *XRCC1*-expression levels in ALN<sup>+</sup> were significantly higher than those in ALN<sup>-</sup> ( $P < 0.05$ , Table 3). Meanwhile, *XRCC1* showed high expression in ER<sup>-</sup>, PR<sup>-</sup>, HER2<sup>+</sup> and low-Ki67-expression

patients, but there was no significant correlation with age, tumor size, or pathological grade (Table 3). As shown in Tables 4 and 5, *XRCC1* expression was not significantly correlated with *XRCC1* rs1799782 polymorphism and molecular subtype of breast cancer.

### *XRCC1* inhibits proliferation and invasion and promotes apoptosis of breast cancer cells

In addition to its DNA-repair function, *XRCC1* has been less studied in oncology. In order to investigate whether *XRCC1* has other effects on breast cancer progression, we constructed an overexpression plasmid of *XRCC1* and overexpressed *XRCC1* in breast cancer cell lines (Figure 2A and B). CCK8 assays showed that in both MCF7 (Figure 2D) and MDA-MB231 (Figure 3A) cell lines, OD values of *XRCC1*-OV cells had significantly decreased after 48 hours' transfection,



**Figure 1** Immunohistochemistry staining showing *XRCC1* expression in breast cancer tissue. **Notes:** (A, B) High *XRCC1* expression; (C, D) low *XRCC1* expression. Magnification  $\times 200$ .

**Table 3** XRCCI-expression association with clinicopathological features of breast cancer

	Cases	XRCCI expression (n)		P-value
		Low	High	
<b>Age, years</b>				>0.05
≥49	71	58	13	
<49	47	30	17	
<b>Tumor size</b>				>0.05
≥2 cm	73	50	23	
<2 cm	45	38	7	
<b>Pathological grade</b>				>0.05
I	13	11	2	
II	72	47	25	
III	33	30	3	
<b>ALN</b>				<0.05
+	50	24	26	
-	68	64	4	
<b>ER</b>				<0.05
Positive	76	70	6	
Negative	42	18	24	
<b>PR</b>				<0.05
Positive	68	65	3	
Negative	50	23	27	
<b>HER2</b>				<0.05
Positive	37	16	21	
Negative	81	72	9	
<b>Ki67</b>				<0.05
High	87	78	9	
Low	31	10	21	

**Abbreviations:** ALN, axillary lymph nodes; ER, estrogen receptor; PR, progesterone receptor.

suggesting that cell proliferation ability decreased significantly. Clone-formation-efficiency assays were performed further to confirm the effect of XRCCI in proliferation. From the results, the clone-formation efficiency of XRCCI-OV cells decreased significantly in MCF7 (Figure 2E and F) and MDA-MB231 (Figure 3B and C) cell lines. Transwell results showed that after transfection of the XRCCI-overexpression plasmid, the number of cells migrating to the lower chamber decreased significantly in MCF7 (Figure 4) and MDA-MB231 (Figure 3D–F) cells, suggesting XRCCI inhibited the migration and invasion ability of breast cancer cells. Furthermore, we performed flow cytometry to estimate cell apoptosis. As shown in Figure 5A and B, cell-apoptosis

**Table 4** XRCCI rs1799782-polymorphism association of XRCCI expression of breast cancer

	Cases	XRCCI rs1799782		P-value
		CC	CT/TT	
High	88	45	43	>0.05
Low	30	13	17	

**Table 5** XRCCI-expression association with molecular subtypes of breast cancer

	Cases	XRCCI expression		P-value
		Low	High	
Luminal A	21	13	8	>0.05
Luminal B	56	42	14	
HER2-positive	32	16	6	
Triple-negative	19	17	2	

in the XRCCI-OV group increased significantly, which proved that XRCCI can promote apoptosis. All the results suggest that high XRCCI expression can inhibit breast cancer progression.

### XRCCI expression increases during inhibition of JNK pathway

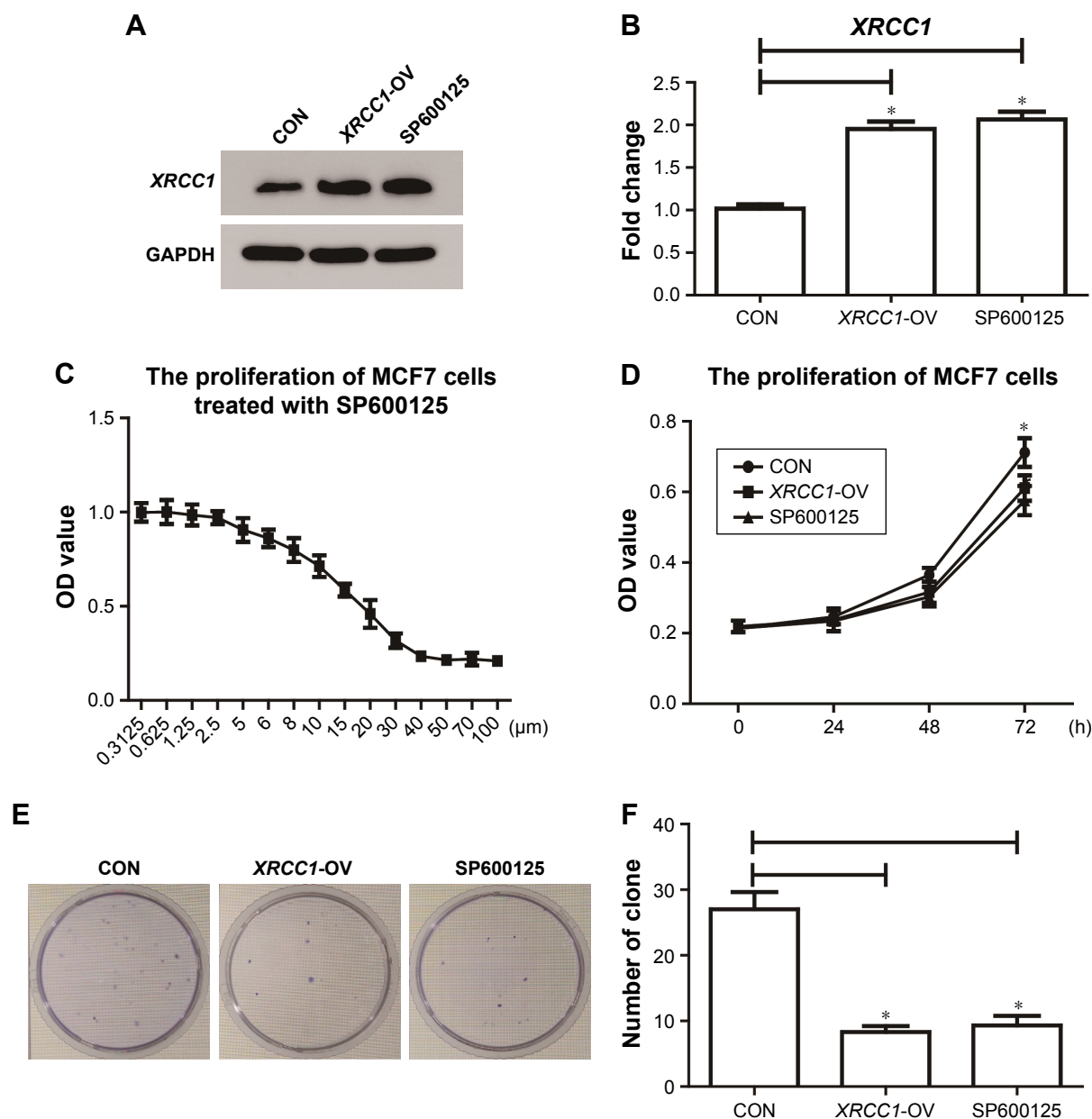
Studies have shown that JNK can regulate DNA repair, so we inhibited the JNK pathway in breast cancer and investigated its role in XRCCI. As shown in Figure 2A and B, cells treated with 10 μM SP600125 for 8 hours showed decreased XRCCI levels and phosphorylation of JNK and STAT3 (Figure 5C–F). Meanwhile, XRCCI overexpression had no effect on the JNK pathway (Figure 5C–F). Therefore, we hypothesized that XRCCI expression is inhibited by the JNK pathway, which can affect tumor progression through XRCCI.

### SP600125 inhibits growth of MCF7 cells

Corresponding to JNK-interference results, we found that the JNK inhibitor SP600125 was able to significantly inhibit the growth of breast cancer cells. The results showed that SP600125 inhibited the proliferation of MCF7 cells in a dose-dependent manner (Figure 2C). The results of CCK8 and clone-formation-efficiency assays revealed that proliferation of MCF7 (Figure 2D–F) and MDA-MB231 (Figure 3A–C) cells treated with SP600125 decreased significantly. Meanwhile, invasion and migration ability decreased significantly (Figures 3D–F and 4) and apoptosis was significantly induced in cells after treatment of SP600125 (Figure 5). These results suggested that SP600125 was a potential drug for breast cancer.

## Discussion

Breast cancer, a malignant tumor with its highest incidence in women, affects physical and mental health, and can even be life-threatening. In recent years, its incidence has continued to grow, accompanied by a trend of younger onset.<sup>9</sup>



**Figure 2** XRCC1 inhibited the proliferation of MCF7 cells.

**Notes:** (A, B) Effect of XRCC1-overexpression plasmid and SP600125. (C) Drug-sensitivity assay of SP600125 in MCF7 cells. (D) CCK8 assay to detect the proliferation of MCF7 cells. (E, F) Clone-formation-efficiency assay. \*P < 0.05.

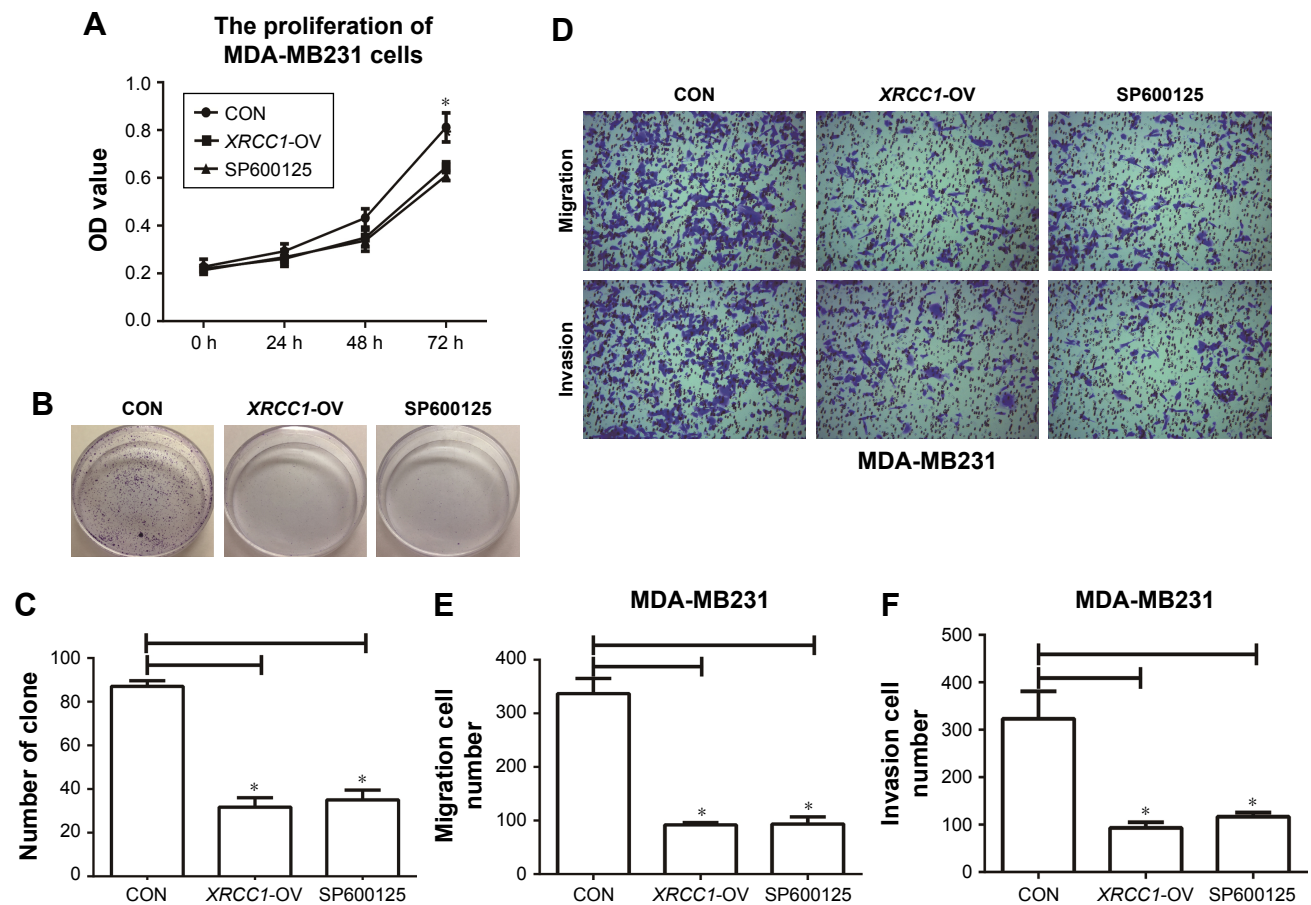
**Abbreviation:** CON, negative control.

Polymorphism of metabolic enzyme genes can lead to differences in metabolic activity. This difference determines that individuals produce different biological effects on environmental chemical carcinogens and mutagens.

XRCC1 is an important component in base-excision and single-strand break repair, which are involved in the process of DNA repair of damage caused by cisplatin or carboplatin.<sup>10</sup> The XRCC1 protein interacts with DNA ligase III to repair the broken DNA strand and with DNA polymerase P to conduct base-excision repair. Studies have demonstrated

that the ability of DNA-repair genes (such as XRCC1) is correlated with the pathogenesis of malignant tumors and drug resistance.<sup>11</sup> XRCC1 polymorphisms are associated with increased susceptibility of breast cancer, lung cancer, gastric cancer, and colorectal cancer.<sup>12-14</sup> There have been three well-studied SNP loci on XRCC1: rs25487 (Arg399Gln), rs1799782 (Arg194Trp), and rs3810378 (Arg280His).<sup>15-17</sup> rs1799782 can affect normal function and expression of the XRCC1 protein and reduce DNA-repair ability. Therefore, we focused on the relationship between this site and the





**Figure 3** XRCC1 inhibited the proliferation, migration, and invasion of MDA-MB231 cells.

**Notes:** (A) CCK8 assays were performed to detect the proliferation of MDA-MB231 cells. (B, C) Clone-formation-efficiency assay. (D) Representative images of transwell assays ( $\times 400$ ). (E) Numbers of migration cells in CON ( $340\pm 35$ ), XRCC1-OV ( $95\pm 5$ ), and SP600125 ( $100\pm 10$ ) groups. (F) Numbers of invasion cells in CON ( $323\pm 76$ ), XRCC1-OV ( $95\pm 5$ ), and SP600125 ( $93\pm 16$ ) groups. \* $P < 0.05$ .

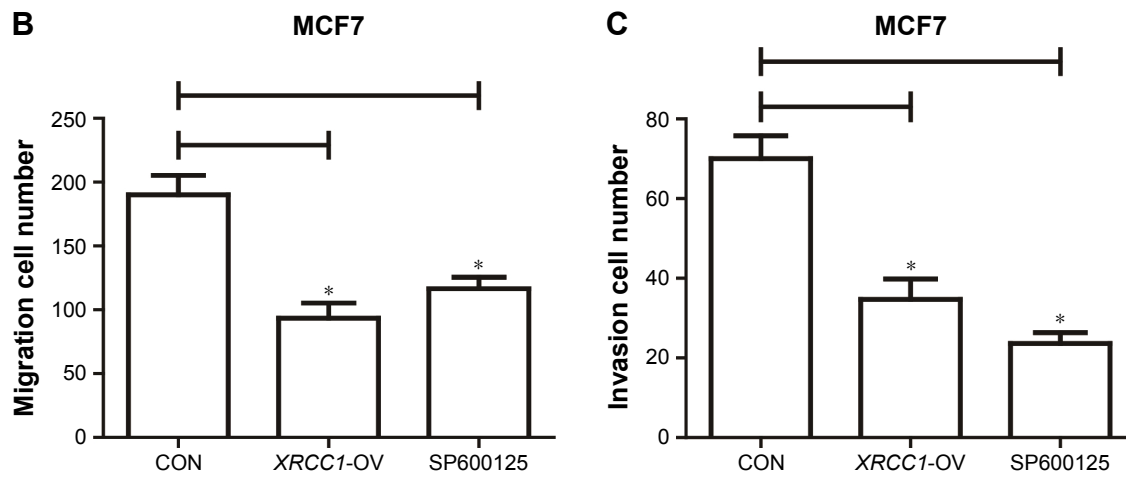
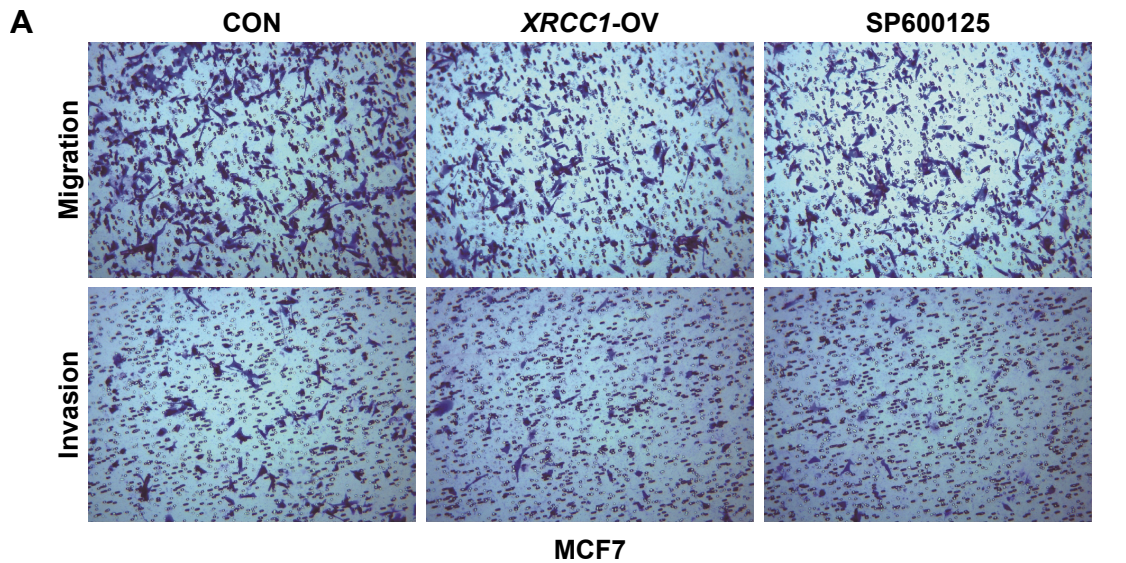
**Abbreviation:** CON, negative control.

pathological features of breast cancer in this study. In this study, there was no association between XRCC1 expression and rs1799782, but they were correlated with distinct molecular subtypes and tumor metastasis in breast cancer.

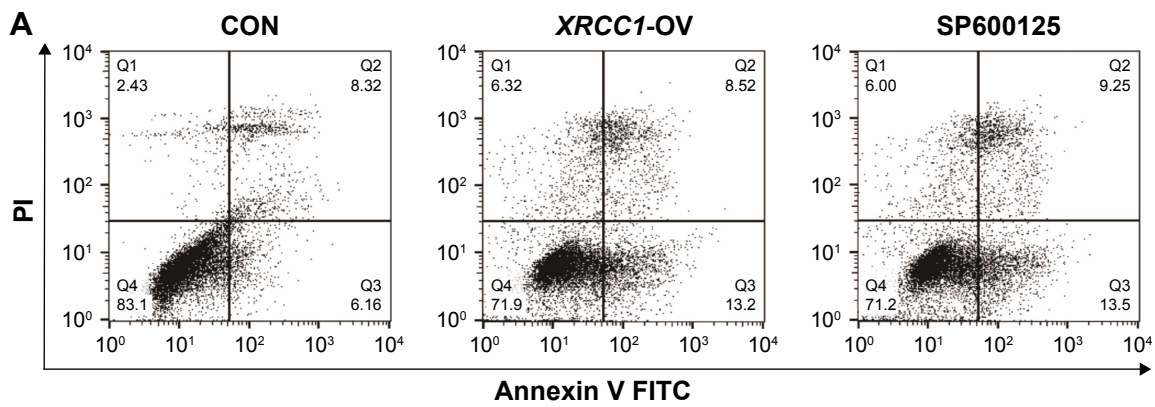
A case-control study of Egyptians demonstrated that XRCC1 Arg399Gln and Arg194Trp genotypes were associated with an increased risk of breast cancer.<sup>18</sup> Two significant SNP loci – XRCC1 Arg399Gln and Arg194Trp – have been found in XRCC1. Changes of amino acid in these two sites were able ultimately to affect XRCC1 protein function and sensitivity of the individual to chemotherapeutic drugs. Wang et al found that patients with Arg194Trp were more sensitive to platinum-based chemotherapy than patients with wild-type alleles in non-small-cell lung cancer.<sup>19</sup> In this study, XRCC1 CT and TT genotypes were in 42.37% and 8.48%, respectively, in 118 patients with breast cancer.

In the present study, we investigated the role of XRCC1 in breast cancer progression. We have proved that XRCC1

can inhibit proliferation and invasion and promote apoptosis of breast cancer cells. XRCC1 expression was regulated by the JNK pathway. Furthermore, we found that the JNK inhibitor SP600125 significantly inhibited the growth of breast cancer cells, marking it as a potential drug for breast cancer. Abnormal activation of JNK-signaling pathway was proved to promote the development of various tumors. Studies have shown that the JNK pathway is overactivated in triple-negative human breast cancer, and this activation can promote tumor growth and metastasis. As such, research on JNK-targeted therapy is one of the foci in clinical transformation medicine for breast cancer.<sup>20</sup> Human breast cancer is the result of a combination of environmental and genetic factors. With the continuous development in sequencing technology, it is possible to detect the genetic background of patients. Therefore, the results of XRCC1-polymorphism research have great application potential in clinical treatment. According to our results, the XRCC1 polymorphism can be

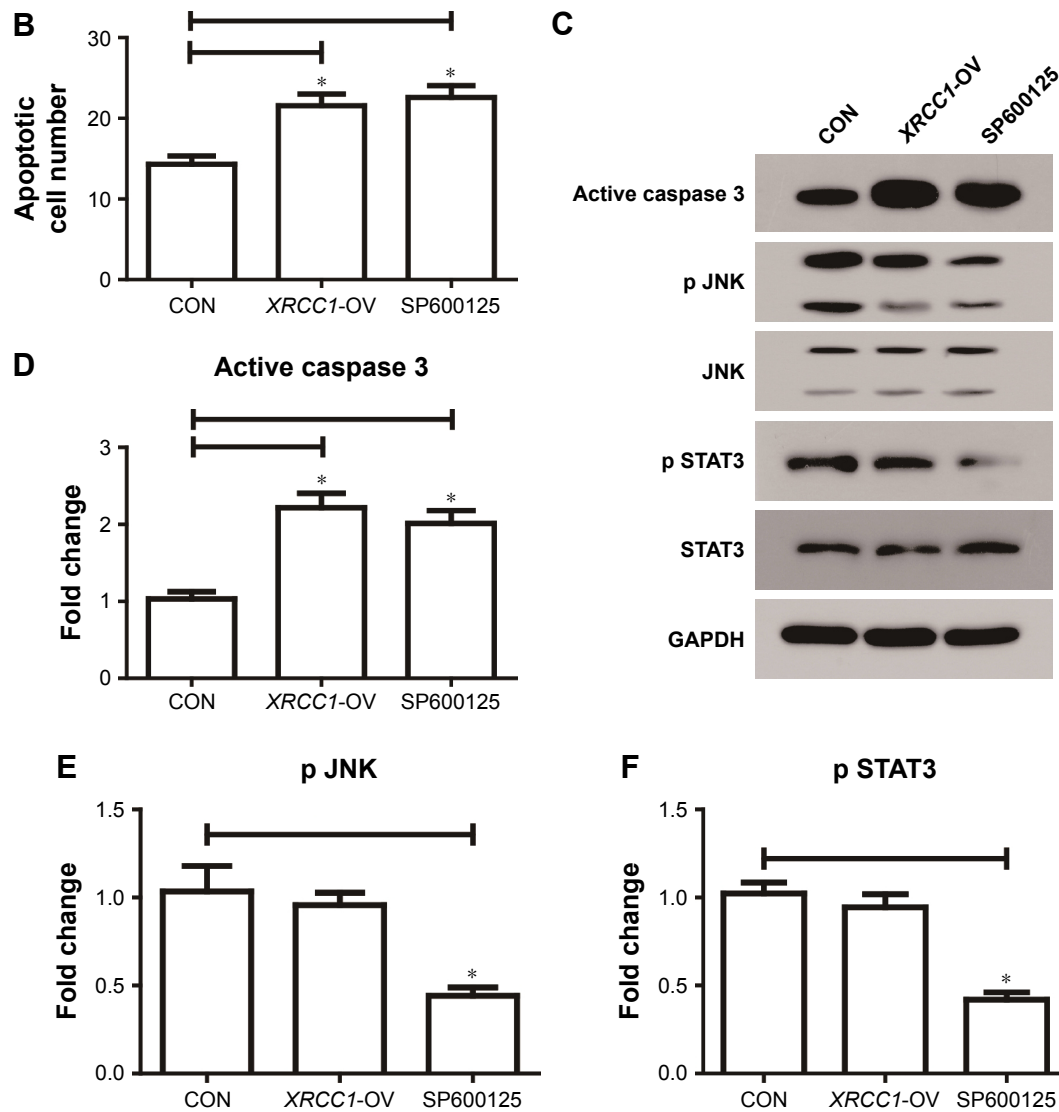


**Figure 4** XRCC1 inhibited migration and invasion of MCF7 cells. **Notes:** Transwell assays were performed to estimate the cell migration and invasion. **(A)** Representative images of transwell assays. Magnification ×400. **(B)** Numbers of migration cells in CON (190±15), XRCC1-OV (90±10), and SP600125 (120±7) groups. **(C)** Numbers of invasion cells in CON (70±8), XRCC1-OV (35±5), and SP600125 (22±2) groups. \*P<0.05. **Abbreviation:** CON, negative control.



**Figure 5** (Continued)





**Figure 5** XRCC1 promoted apoptosis of MCF7 cells.

**Notes:** (A) Apoptotic cell numbers of each group were examined by flow cytometry. (B) Number of apoptotic cells in CON, XRCC1-OV, and SP600125 group. (C–F) Western blot results of active caspase 3 and JNK pathway-related genes. \* $P < 0.05$ .

**Abbreviations:** CON, negative control; FITC, fluorescein isothiocyanate; PI, propidium iodide.

used as a marker for differentiating the susceptibility of different types of breast cancer, and its effect on breast cancer can be inhibited by the JNK-signaling pathway.

## Conclusion

Polymorphisms of susceptibility genes in breast cancer have positive clinical implications for our understanding of gene mutations in regional breast cancer patients.<sup>21,22</sup> We expect case–control studies with large samples, high quality, good uniformity, and multicenter collaboration to evaluate the relationship between these polymorphisms and susceptibility to breast cancer, and to provide more reliable evidence and basic research for the prevention and treatment of breast cancer.

Obviously, the failure of chemotherapy is not caused by a single factor. It is a complex network and a combination of multiple cellular pathways and molecular mechanisms. Therefore, there is still much for us to explore.

## Acknowledgments

This research was supported by the Natural Science Foundation of Shandong Province (ZR2012HL04) and the Shandong Provincial Science and Technology Development Plan (2012YD18062).

## Disclosure

The authors report no conflicts of interest in this work.

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