# The fibroblast growth factor receptor 2-mediated extracellular signal-regulated kinase 1/2 signaling pathway plays is important in regulating excision repair cross-complementary gene 1 expression in hepatocellular carcinoma

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**Abstract.** Excision repair cross-complementary gene 1 (ERCC1) is a downstream regulatory target of fibroblast growth factor receptor 2 (FGFR2); however, the mechanism of its action has not been elucidated. The cascades downstream of FGFR2 include the PKC, Ras/Raf/MEK/ERK, JAK/STAT and PI3K pathways. ERCC1 is considered to be a closely related downstream target gene of extracellular signal-regulated kinase (ERK)1/2, since ERCC1 mRNA and protein levels may be inhibited by the ERK inhibitor U0126. It was hypothesized that FGFR2, which specifically binds with fibroblast growth factor 7 (FGF7), may regulate ERCC1 gene expression through the ERK signaling pathway. The aim of the present study was to explore the association between the regulatory effect of FGFR2 on ERCC1 gene expression and the p-ERK1/2 signaling pathway in a drug-resistant hepatocellular carcinoma (HCC) cell line. The drug-resistant cell line HepG2/OXA and its parental cell line HepG2 were transfected with Bek shRNA in the logarithmic growth phase. Transfected and untransfected HepG2 and HepG2/OXA cells were then stimulated with FGF7 and changes in the protein expression of FGFR2, p-ERK1/2 and ERCC1 was detected with western blot analysis. Following transfection, HepG2/T and HepG2/OXA/T cells were observed to grow stably in a screening medium containing puromycin. The western blot analysis demonstrated a significant decrease in the protein expressions of FGFR2, p-ERK1/2 and ERCC1 in HepG2/T and HepG2/OXA/T cells as compared to untransfected cells. Expression of FGFR2, p-ERK1/2 and ERCC1 in HepG2/OXA cells was significantly increased compared to the parental HepG2 cells. Following stimulation with FGF7, the expression of FGFR2, p-ERK1/2 and ERCC1 was increased, with significant differences between HepG2 and HepG2/OXA cells in the expression of p-ERK1/2 and ERCC1. No differences were detected in the protein levels following Bek shRNA transfection in HepG2/T and HepG2/OXA/T cells. In conclusion, the FGFR2-mediated ERK1/2 signaling pathway in HCC cells plays an important role in the regulation of ERCC1 expression.

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*Key words:* fibroblast growth factor receptor 2, excision repair cross-complementary gene 1, extracellular signal-regulated kinase, hepatocellular carcinoma

## Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors. It currently ranks fifth among malignant tumors, accounting for >626,000 cases of cancer annually and ranks third among tumor-related deaths, with 600,000 mortality cases per year (1-2). HCC is prevalent in China, accounting for 55% of new cancer cases and ranks second only to lung cancer regarding tumor-related mortality. Since early symptoms are not apparent in HCC, the majority of patients are admitted to hospital at a later stage, with liver cirrhosis being the presenting symptom in 85-95% of the cases. The success rate of radical surgical resection is low (<20%) and the recurrence rate following radical resection is 35-50%. For the majority of advanced HCC patients with a poor prognosis, conservative treatment methods are the primary choice (3). Consequently, there is a need to improve treatment efficacy for these patients.

Human fibroblast growth factor receptor 2 (FGFR2), which is the Bek oncogene expression product, has a high affinity for a variety of FGFs, including fibroblast growth factor 7 (FGF7) (4). A previous study demonstrated that expression of FGF and FGFR was increased in HCC patients (5). Harimoto *et al* (9) also demonstrated that FGFR2 plays an important role in HCC differentiation, with the expression of FGFR2 being 4.7 times higher in poorly differentiated HCCs. A high expression of FGFR2 is closely associated with the incidence of portal vein tumor thrombosis, increased α-fetoprotein levels and shortened

overall survival rates and disease-free survival periods, suggesting the significance of FGFR2 in HCC development. In addition, targeted FGFR2 treatment exhibited therapeutic effects in related studies. Bai *et al* (10) investigated the role of FGFR2 signaling *in vivo* and *in vitro* using GP369, which is an FGFR2-IIIb-specific antibody and the results indicated that GP369 inhibited FGFR2 ligand phosphorylation and its relative protein expression in downstream signaling pathways, thus suppressing FGFR2-induced cell proliferation. Abnormal FGFR2 signaling is crucial for tumorigenesis and tumor development and GP369 exhibited potential therapeutic value for patients with abnormal FGFR2 signal activation. Therefore, FGFR2 may be used as an effectively adverse indicator for HCC prognosis and as a new molecular target in therapeutic treatment strategies.

A previous study from our research group (11) demonstrated that the FGFR2 inhibitor Ki23057, combined with chemotherapeutics, may exert obvious synergistic effects on the high-expressing FGFR2 gastric carcinoma drug-resistant cell lines OCUM-2M/SN38, OCUM-2M/PTX and OCUM-2M/VP16, by downregulating the expression of the excision repair cross-complementary gene 1 (ERCC1). This provided evidence that ERCC1 is a target gene in the downstream pathway regulated by FGFR2; however, the detailed mechanism has not been elucidated. In combination with their receptors, FGFs are able to phosphorylate intracellular tyrosine residues on target proteins and accordingly activate signaling pathways through a variety of intracellular signal transduction molecules. The FGF-induced downstream cascade includes the PKC, Ras/Raf/MEK/ERK, JAK/STAT and PI3K pathways (12). ERCC1 is considered to be a closely related downstream target gene of ERK1/2, since ERCC1 mRNA and protein levels may be inhibited by the ERK inhibitor U0126 (13). We hypothesized that FGFR2, specifically binding with FGF7, may regulate ERCC1 gene expression through the ERK signaling pathway. This study aimed to verify the hypothesis that the expression of the ERCC1 gene is associated with FGFR2-mediated ERK1/2 signaling, through the upregulation of FGF7 and the downregulation of FGFR2 using shRNA gene silencing in HepG2/OXA cell models.

## Materials and methods

### *Cell culture*

*Human HCC cell line HepG2*. Human HCC HepG2 cells were conventionally cultured in a high-glucose Dulbecco's modified Eagle's medium (Gibco BRL, Carlsbad, CA, USA) supplemented with 100 U/ml penicillin, 100 $\mu$g/ml streptomycin and 10% fetal bovine serum (Hangzhou Sijiqing Biotec Co., Zhejiang, China) at 37˚C in a 5% $CO_2$ incubator. Confluent culture flasks were subcultured by using 0.25% trypsin (Guge Biology Co., Wuhan, China) and were used in experiments after reaching 70-80% confluence.

*HepG2/OXA-resistant cell line*. An oxaliplatin (OXA)-resistant subline was established by discontinuously exposing parental HepG2 cells to a high-OXA concentration (25 $\mu$M) medium over the course of one year until the resulting cells were able to grow exponentially in a medium containing 1 $\mu$M OXA. The drug-resistant HepG2/OXA cell line (HepG2/OXA) in a logarithmic growth phase was conventionally cultured in a culture medium containing 1 $\mu$mol/l OXA (Sigma Aldrich, St. Louis, MO, USA). Prior to protein lysis, HepG2/OXA cells were subcultured for three generations in OXA-free medium.

*Short hairpin RNA for Bek gene (Bek shRNA) cell transfection in HepG2 and HepG2/OXA cells*. Cell transfections were performed using Bek shRNA plasmid (h) (sc-29218-SH kit; Santa Cruz Biotechnology, Inc., Santa Cruz, CA, USA), according to the manufacturer's instructions. HepG2/OXA and HepG2 cells were cultured in 6-well culture plates and were then supplemented with antibiotic-free growth medium containing fetal bovine serum, until they reached 60-80% confluence. Using a sample injector, shRNA plasmid DNA solution (solution A) was directly added into the diluted shRNA plasmid transfection reagent (solution B). The mixture was gently triturated and then incubated at room temperature for 30 min. The samples were rinsed twice with 2 ml shRNA transfection medium to absorb the matrix and 0.8 ml shRNA plasmid transfection medium was added to each well. A 200-$\mu$l drop of shRNA plasmid and DNA/shRNA plasmid transfection reagent mixture was added and cells were incubated at a 37˚C incubator for 8 h, followed by incubation with 1 ml growth medium containing twice the concentration of normal serum (twice normal culture medium) and antibiotics for an additional 24 h. After a 48-h transfection, the culture medium was discarded and cells were incubated in a medium containing 2 $\mu$g/ml puromycin dihydrochloride (sc-108071, Santa Cruz Biotechnology Inc.). The screening medium was replenished every 2 days until cells could be stably cultured. Cells were then rinsed twice with phosphate-buffered saline and lysed in 300 $\mu$l of 1X electrophoresis buffer solution, with gentle agitation and trituration prior to SDS-PAGE gel electrophoresis.

*Experimental grouping*. HepG2, HepG2/T, HepG2/OXA and HepG2/OXA/T cells were conventionally cultured in culture flasks. After reaching 60% confluence, cells were incubated with a culture medium containing a final concentration of 5 ng/ml FGF7 (Santa Cruz Biotechnology) for 24 h. Cells were trypsinized and lysed and the protein concentration was measured with the BCA method and adjusted to 1 $\mu$g/$\mu$l protein percentage. Cells cultured in FGF7-free culture medium were used as a control.

*Western blot assay for FGFR2, ERCC1, p-ERK1/2 and β-actin expression*. The expression levels of FGFR2, ERCC1, p-ERK1/2 and β-actin were determined with western blot analysis on NC membranes (Amersham Pharmacia Biotech, Inc., Piscataway, NJ, USA). p-ERK1/2 rabbit anti-monoclonal antibody (sc-16982-R) and ERCC1 mouse monoclonal antibody were purchased from Santa Cruz Biotechnology Inc. FGFR2 mouse monoclonal antibody (MAB684) was purchased from R&D Systems, Inc. (Minneapolis, MN, USA). Secondary antibody staining was performed using Dylight™ 800-labeled anti-rat IgG (H+L) and anti-rabbit IgG (H+L) antibodies (Gaithersburg Biotechnology, Gaithersburg, MD, USA).

*Statistical analysis*. Data were expressed as the means ± standard deviation (SD) and differences between groups were

Table I. FGFR2 protein expression concentrations in HepG2, HepG2/OXA, HepG2/T and HepG2/OXA/T cells (n=5).

| Groups | HepG2 | HepG2/OXA | HepG2/T | HepG2/OXA/T |
|---|---|---|---|---|
| Control | 0.7228±0.0230[c,d] | 0.9566±0.0457[a] | 0.0108±0.0061[a] | 0.1040±0.0170[c] |
| FGF7 | 0.7818±0.0821 | 1.1156±0.1117[b] | 0.0112±0.0033 | 0.1070±0.0181 |

[a]P<0.01 vs. the HepG2 control group; [b]P<0.05, [c]P<0.01 vs. the HepG2/OXA control group; [d]P<0.01 vs. the HepG2/T control group. FGFR2, fibroblast growth factor receptor 2; FGF7, fibroblast growth factor 7; OXA, oxaliplatin.

Table II. pERK1/2 protein expression concentrations in HepG2, HepG2/OXA, HepG2/T and HepG2/OXA/T cells (n=5).

| Groups | HepG2 | HepG2/OXA | HepG2/T | HepG2/OXA/T |
|---|---|---|---|---|
| Control | 1.4270±0.0807[c,d] | 1.9368±0.0918[a] | 0.1390±0.0351[a] | 0.4846±0.0719[c] |
| FGF7 | 1.7596±0.0953[a] | 2.1040±0.1263[b] | 0.1576±0.0325 | 0.5056±0.0360 |

[a]P<0.01 vs. the HepG2 control group; [b]P<0.05, [c]P<0.01 vs. the HepG2/OXA control group; [d]P<0.01 vs. the HepG2/T control group. FGF7, fibroblast growth factor 7; OXA, oxaliplatin.

compared by one-way analysis of variance using SPSS17.0 statistical analysis software (SPSS, Inc., Chicago, IL, USA), whereas intragroup comparisons were performed with the Student's t-test. P<0.05 was considered to indicate a statistically significant difference.

## Results

*Identification of Bek shRNA-transfected cells*. HepG2 and HepG2/OXA cells transfected with Bek shRNA were stably grown in a screening medium containing puromycin. Western blot analysis identified a significant decrease in the expression of FGFR2 protein, indicating the successful downregulation of the protein (Fig. 1).

*Expression of FGFR2 protein in HepG2, HepG2/OXA, HepG2/T and HepG2/OXA/T cells*. Compared to the parental HepG2 cells, FGFR2 expression in HepG2/OXA cells was significantly increased (Fig. 1; P<0.05). After HepG2 and HepG2/OXA cells were transfected with Bek shRNA, FGFR2 protein expression was significantly decreased in HepG2/T and HepG2/OXA/T cells (Table I; P<0.01). After cells were stimulated with FGF7, FGFR2 expression was increased in the untransfected cells; however, these differences were not statistically significant compared to the unstimulated control counterparts (P>0.05; Table I, Fig. 2).

*Expression of pERK1/2 protein in HepG2, HepG2/OXA, HepG2/T and HepG2/OXA/T cells*. Compared to the parental HepG2 cells, pERK1/2 expression in HepG2/OXA cells was significantly increased (P<0.01). Following transfection with Bek shRNA, the pERK1/2 protein expression in HepG2/T and HepG2/OXA/T cells was significantly decreased (P<0.01), compared to the untransfected controls. Following stimulation with FGF7 in HepG2 and HepG2/OXA cells, the expression of pERK1/2 was upregulated and the differences were statistically significant (P=0.00034 and 0.04359, respectively). In

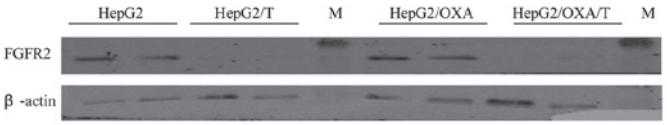


Figure 1. Fibroblast growth factor receptor 2 (FGFR2) protein expression following Bek shRNA transfection in HepG2 and HepG2/oxaliplatin (OXA) cells.

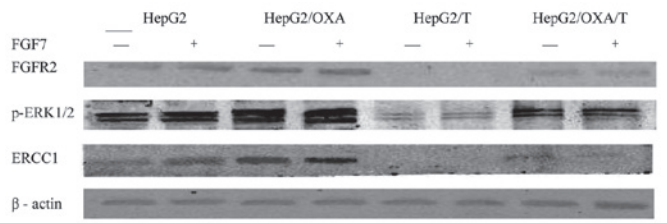


Figure 2. Comparison of fibroblast growth factor receptor 2 (FGFR2), p-ERK1/2 and excision repair cross-complementary gene 1 (ERCC1) protein expression concentrations before and after fibroblast growth factor 7 (FGF7) stimulation.

HepG2/T and HepG2/OXA/T cells, FGF7 stimulation did not significantly affect pERK1/2 (P>0.05; Table II, Fig. 2).

*ERCC1 protein expression in HepG2, HepG2/OXA, HepG2/T and HepG2/OXA/T cells*. ERCC1 expression in HepG2/OXA cells increased significantly compared to the parental HepG2 cells (P<0.01). Following HepG2 and HepG2/OXA cell transfection with Bek shRNA, ERCC1 protein expression in HepG2/T and HepG2/OXA/T cells was significantly decreased (P<0.01). FGF7 stimulation upregulated the expression of ERCC1 in the HepG2/OXA cells and, to a lesser extent, in HepG2 cells, with statistically significant differences (P=0 and 0.02436, respectively). FGF7 stimulation upregulated ERCC1 expression in HepG2/T and HepG2/OXA/T cells; however, the difference was not statistically significant (P>0.05; Table III, Fig. 2).

Table III. ERCC1 protein expression concentrations in HepG2, HepG2/OXA, HepG2/T and HepG2/OXA/T cells (n=5).

| Groups | HepG2 | HepG2/OXA | HepG2/T | HepG2/OXA/T |
|---|---|---|---|---|
| Control group | 0.4328±0.0548[c,d] | 1.5498±0.0709[a] | 0.0138±0.0054[b] | 0.1382±0.0277[c] |
| FGF7 | 1.1100±0.0841[a] | 1.745±0.1403[b] | 0.0116±0.0050 | 0.1120±0.0305 |

[a]P<0.01 vs. the HepG2 control group; [b]P<0.05, [c]P<0.01 vs. the HepG2/OXA control group; [d]P<0.01 vs. the HepG2/T control group. FGF7, fibroblast growth factor 7; OXA, oxaliplatin.

## Discussion

ERCC1 is the key rate-limiting enzyme in the nucleotide excision repair (NER) pathway and is closely associated with the progression of HCC and drug resistance. Fautrel *et al* (5) reported an increase in ERCC1 expression in fibrotic compared to normal liver tissue and the expression of ERCC1 protein concentration was significantly increased in HCC tissue concomitant with hepatic fibrosis, compared to HCC tissue without fibrosis. These findings suggest that ERCC1 plays an important role in liver fibrosis and HCC. ERCC1 may predict the sensitivity of platinum-based chemotherapeutic drugs and has been widely used in the treatment of lung cancer in large-scale phase III clinical trials. Consequently, lung cancer patients with high ERCC1 expression levels should avoid the use of platinum-based chemotherapeutic drugs, which has been formulated in the NCCN guidelines.

In HCC, the DNA repair pathway and its rate-limiting enzyme ERCC1 were highly expressed in HCC cell lines, even without chemotherapeutic stimulation. Ueda *et al* (6) reported that ≤33% of HCC tissues presented with a high expression of ERCC1, which was associated with cisplatin resistance. Our experimental findings indicated that in the OXA-resistant HCC cell line HepG2/OXA, the expression of ERCC1 was significantly increased compared to that in the parental cell line HepG2. This finding is inconsistent with previous experimental results (14). This difference may indicate that xeroderma pigmentosum group C (XPC), rather than ERCC1, determines the DNA damage repair in the HepG2 cell lines and the discrepancies may be due to the selection of drugs used to induce DNA damage (7). Further investigation is required to elucidate the mechanism of regulation of ERCC1 expression, which may contribute to the development of platinum-resistant drugs for the reversal of HCC and to the enhancement of the efficacy of HCC treatment.

In view of the mechanisms that regulate the expression of ERCC1, the present study demonstrated that, since the ERCC1 promoter region may bind to a variety of transcription factors, numerous external factors may induce the expression of ERCC1. However, the specific molecular mechanisms may vary in different types of tumor cells. Youn *et al* (15) reported that cisplatin-resistant cells may upregulate the transcription factor AP1 through the H-ras oncogene and increase ERCC1 expression. Wilson *et al* (16) observed that the transcription factor Ets-1 regulates ERCC1 expression in ovarian cancer cells and Ets-1 and c-Fos exert synergistic effects (17). Our previous study results demonstrated that in the drug-resistant gastric cancer cell lines OCUM-2M/SN38, OCUM-2M/PTX and OCUM-2M/VP16, Ki23057 monoclonal antibody targeting of FGFR2 downregulated ERCC1 expression, indicating that ERCC1 is an FGFR2 downstream-regulated target gene (11). In the present study, it was demonstrated that, compared to parental HepG2 cells, FGFR2 expression in HepG2/OXA cells was significantly increased. Following shRNA gene silencing, FGFR2 was significantly decreased and the ERCC1 protein expression in HepG2/T and HepG2/OXA/T cells was also significantly inhibited, suggesting that ERCC1 is another FGFR2 downstream-regulated target gene. However, additional investigations are required to completely elucidate its function.

FGFR2 is the product of the Bek oncogene expression product and a transmembrane tyrosine kinase receptor with a high affinity for a variety of FGFs (8). Studies have demonstrated (13) that ERCC1 in HCC cells is the downstream target of MEK/ERK and PI3K. When exposed to epidermal growth factor, NER activity and ERCC1 expression increase in normal liver and HCC cells in conjunction with ERK1/2 and the EFG-mediated activation of ERCC1 may be inhibited by U0126 and ERK1/2 siRNA silencing. Furthermore, basically expressed ERCC1 may be inhibited by a PI3K inhibitor, FKBP12, rapamycin-associated protein shRNA or rapamycin-targeting PI3K kinase (18). In this study, we observed that the multidrug resistant cell line HepG2/OXA and its parental cell line HepG2 exhibited high expression levels of FGFR2 and ERCC1, as well as a significant increase in ERK1/2. Following shRNA silencing of FGFR2, accompanied by a decrease in phosphorylated ERK1/2 expression, ERCC1 expression was significantly inhibited, indicating that the ERK1/2 pathway plays an important role in the regulation of FGF7/FGFR2-mediated ERCC1 expression.

In summary, the FGFR2-mediated ERK1/2 signaling pathway is critical for the regulation of ERCC1 expression. We investigated the FGFR2-mediated ERK1/2 signaling pathway in a broader attempt to identify new pathways for ERCC1 regulation, inhibition of DNA injury repair and the reinforcement of platinum drugs.

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