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LAB INVESTIGATION

Single nucleotide polymorphisms and expression of ERCC1 and ERCC2 vis-à-vis chemotherapy drug cytotoxicity in human glioma

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Abstract ERCC1 and ERCC2 have been known to belong to the nucleotide excision repair (NER) pathway and are essential to the repair of cisplatin DNA adducts. In the present study, we have examined the potential correlation of ERCC1, ERCC2 mRNA expression and single nucleotide polymorphism (SNP) to chemotherapy drug cytotoxicity from 49 human gliomas. Fresh human glioma specimens were obtained during surgery. SNPs of ERCC1 and ERCC2 was determined by single strand conformation polymorphism (SSCP) and sequencing. ERCC1 and ERCC2 expression was quantified using real-time quantitative reverse transcription-PCR. Chemotherapy drug cytotoxicity was determined by the tetrazolium (MTT) assay for cisplatin (CDDP), 1,3-bis-(2-chloroethyl)-1-nitrosourea (BCNU), vincristine (VCR) and teniposide (VM26). The results show that there was no statistically significant association between the C8092A polymorphism of ERCC1 or codon 312 and codon 751 polymorphisms of ERCC2 and the chemotherapy drug cytotoxicity. However there was a strong correlation between ERCC1 and ERCC2 mRNA expression levels (Spearman $r = 0.42$; $P < 0.003$). Further more, tumor samples with low ERCC1 mRNA expression levels showed enhanced CDDP cytotoxicity ($P = 0.0001$) while ERCC2 expression was reversely correlated with BCNU cytotoxicity ($P = 0.004$). In sum, Our results indicated that ERCC1 mRNA expression is associated with CDDP cytotoxicity and ERCC2 mRNA levels is related with BCNU cytotoxicity, while there was no correlation between SNP of ERCC1, ERCC2 and *in vitro* cytotoxicity of four anticancer drugs, CDDP, BCNU, VCR and VM26.

Keywords ERCC1 · ERCC2 · NER · Glioma · SNP

Abbreviations

BCNU	1,3-bis-(2-chloroethyl)-1-nitrosourea
CDDP	Cisplatin
DMSO	Dimethylsulfoxide
ERCC1	Excision repair cross complementing protein 1
ERCC2	Excision repair cross complementing protein 2
HDRA	Histoculture drug response assay
MTT	Tetrazolium
NSCLC	Non-small cell lung cancer
NER	Nucleotide excision repair
PPC	Peak plasma concentration
SNP	Single nucleotide polymorphism
SSCP	Single strand conformation polymorphism
SarCNU	(2-chloroethyl)-3-sarcosinamide-1-nitrosourea
VCR	Vincristine
VM26	Teniposide

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Introduction

Drug resistance is an enormous challenge for neuro-oncologist to treat the patients with gliomas. Understanding molecular mechanisms of drug resistance could be key to solve this problem, but studies using cell lines may not be good representation for patients while clinical chemotherapeutic response may affected by many factors. The histoculture drug response assay (HDRA) is an important in vitro chemosensitivity test [1, 2] and the clinical efficacy of chemotherapy has been shown to have a strong correlation with HDRA data in various kinds of solid tumor [2, 3].

The NER (nucleotide excision repair) pathway is a complex network of many proteins assembled in DNA repair system and there are about 16 essential proteins involved in DNA-damage recognition and excision. ERCC1 is primarily involved in the recognition and excision of cisplatin DNA adduct and further repair steps are followed by some genes including helicase ERCC2 that is a component of transcription factor TFIIH. Increased removal of these cisplatin adducts by NER pathway leads to drug resistance of cancer cells to cisplatin-based chemotherapy, and NER-deficient cells are hypersensitive to cisplatin [4]. It has shown that high ERCC1 expression in tumor tissue has been related to CDDP resistance in ovarian cancer [5], gastric cancer [6], NSCLC (non-small cell lung cancer) [7]. Low levels of ERCC1 expression correlated significantly with longer survival in gemcitabine–cisplatin-treated advanced NSCLC patients [8]. It has also observed that ERCC2 overexpression led to CDDP and BCNU or (2-chloroethyl)-3-sarcosinamide-1-nitrosourea (SarCNU) resistance in some human tumor cell lines [9-11] although that was not found in some other cell lines [12, 13]. ERCC1 and ERCC2 mRNA differential expression pattern lies between malignant and nonmalignant brain tissue [12]. In addition, the mRNA levels of ERCC1 are significantly related to those of ERCC2 [14].

SNP is a point mutation carried by some individuals of a population. Recently, SNPs have been confirmed as predictive markers of treatment response, toxicity and survival in cancer patients. About 20–32% of nonsynonymous SNPs in coding regions of NER genes may alter protein structure, function, stability or folding [15, 16]. Reports have shown that common polymorphisms in the ERCC1 and ERCC2 gene may be associated with differential DNA repair capacity in gliomas [17, 18]. The polymorphism of ERCC1 C8092A SNP has been associated with altered mRNA levels and stability [19] and overall survival with cisplatin-based chemotherapy [20]. But studies regarding to two polymorphisms in the ERCC2 gene, codon312G/A and codon751A/C and overall survival with cisplatin-based chemotherapy have yielded diverging results [21, 22].

In order to elucidate the relationship of SNPs and gene expression with chemotherapy drug response, SSCP and sequencing assay have been applied to test ERCC1, ERCC2 SNPs in human glioma samples. We also examined ERCC1and ERCC2 mRNA expression by real-time reverse transcription PCR (RT-PCR).

Materials and methods

Patients

A total of 61 fresh samples were obtained from patients with newly diagnosed primary glioma at Cancer Center, Sun Yet-sen University between February 2005 and December 2005. Tumor samples were immediately submitted for cell culture and drug cytotoxicity testing. Forty nine specimens were successfully analyzed by HDRA, with a technical success rate of 80%. These samples were from primary surgery glioma without radiation or chemotherapy. Tumor sampling was performed specifically for in vitro testing and was approved by the Research Ethical Committee, Sun Yet-sen University. Patients were told that samples were tested for the purpose of identifying chemotherapy regimens with above and below average probabilities of providing clinical benefit on a non-investigational basis. However, in practice, more than 60% of patients finally abandon managing the chemotherapy after the surgery because of cost or other reasons. Data from 49 patients were available for correlating SNP and expression of ERCC1 and ERCC2 and in vitro sensitivity. Baseline patient characteristics are shown in Table 1. Meanwhile five glioma cell lines T98G, SF767, UW28, MGR1 and MGR2 were also analyzed for the status of SNPs.

Laboratory methods

HDRA In vitro chemotherapy drug response was performed as reported by Furukawa et al [1, 23]. Briefly, glioma specimens surgically resected from patients were dissociated using collagenase and dispersed as described [24]. Tumor cells were cultured in complete medium with anticancer drug at final concentration of peak plasma concentration (PPC), followed by incubation at 37°C for 7 days. After 7 days of incubation, RPMI 1640 containing 0.2% MTT (Sigma) were added to each well. The plate was then incubated for additional 24 h. The supernatant in each well was aspirated carefully and

Table 1 Clinical data and in vitro chemotherapy drug response in 49 patients

Characteristics	*N* (%)
Age(years)	
Median(range)	31 (4–69)
Gender	
Male	27 (44.9)
Female	22 (55.1)
Histology of the tumor	
Glioblastoma multiforme	5 (10.2)
Anaplastic Astrocytoma	31 (63.3)
Oligoastrocytoma	1 (2.0)
Others	12 (24.5)
Sensitive Response (IR ≥ 50%)	
CDDP	15 (30.6)
BCNU	8 (16.3)
VCR	8 (16.3)
VM26	15 (30.6)

dimethylsulfoxide (DMSO, Sigma) was added for solubilizing the MTT-formazan. After another 4 h of incubation, MTT-formazan solution from each well was transferred to a 96-well microplate and the absorbance of each well was read on a microplate reader (Bio-Rad Instruments, USA) at a test wavelength of 550 nm. Four anticancer drugs from commercial sources were used: CDDP, BCNU, VCR and VM26. The chemotherapy drug response rate (inhibition rate, IR) was calculated as follows [3]: IR (%) = (1-mean absorbance for drug-treated tumor/ mean absorbance for control) × 100. Anticancer drugs, which showed an IR value of more than 50%, were considered as sensitive, however, the efficacy of drugs that caused infections or those with an OD of 0.1 or less in a control group could not be determined.

SNP testing Genomic DNA was extracted from tissue samples using a QIAamp® DNA mini kit (Qiagen Inc.), following the manufacturer's protocol. PCR-SSCP assay and DNA sequencing were used to determine the frequency of ERCC1 and ERCC2 polymorphisms. The SSCP method for genotyping polymorphisms has been described [19]. The genomes of ERCC1 (C8092A) and ERCC2 (codons 312G/A and 751A/C) were amplified in a PCR using the primers as follows: ERCC1 C8092A forward, 5′-GGA GGG ATT CTG GGG GTG TCA C-3' and reverse, 5'-GCA GAG TCA GGA AAG CCG GAT G-3′. ERCC2 Asp312Asn forward, 5′-GAG TAC CGG CGT CTG GTG GA-3′ and reverse, 5′-ACG GGG AGG CGG GAA AGG GA-3′; ERCC2 Lys751Gln forward, 5′-CCC CTC TCC CTT TCC TCT GT-3′ and reverse, 5′-CCA GGA ACC GTT TAT GGC C-3′. The 25 μl PCR reaction consisted of 30–50 ng genomic DNA, 0.2 mM dNTPs, 5 pmol each primer, and one unit of Taq DNA polymerase (TaKaRa Biotechnology Dalian Co., Ltd, China) in the manufacturer's buffer. Negative controls lacking DNA templates were set up with all PCR reactions. PCR were started at 94°C for 4 min, followed by 35 cycles of 94°C for 30 s, 61°C for 30 s, and 72°C for 30 s, and a final elongation step at 72°C for 7 min.

Direct sequencing of PCR fragments was performed on representative DNA samples of different migration patterns on SSCP gel to determine the corresponding DNA sequences using a 3100 ABI automated sequencer (Applied Biosystems, Foster City, CA).

Determination of ERCC1 and EERCC2 expression Total cellular RNA was extracted using Trizol (Invitrogen Corporation, Carlsbad, CA, USA) and 1 μg RNA was reverse transcribed using an oligo(dT)18 primer and AMV reverse transcriptase(TaKaRa Biotechnology Co., Ltd, Dalian, China) according to the manufacturer's recommendations.

After cDNA synthesis ERCC1, ERCC2 expression was analyzed with real-time quantitative PCR. Quantification of gene expression was performed using the ABI Prism 7000HT Sequence Detection System (Applied Biosystems, Foster City, CA). The primer and probe sets were designed using Primer Express 2.0 Software (Applied Biosystems, Foster City, CA). The primers and labeled probes were as following: β-actin, forward 5′-GCT CAC CAT GGA TGA TGA TATC-3′, reverse 5′-GCC AGA TTT TCT CCA TGT CGTC -3′ and probe FAM-5′-CAA CGG CTC CGG CAT GTG C-3′-TAMRA; ERCC1, forward 5'-CAG CAA GGA AGA AAT TTG TGA TAC C -3′, reverse 5′- CAG TGG GAA GGC TCT GTG TAG AT-3′, probe 5′-CCT CCT GGA GTG GCC AAG CCC TTA T-3′; ERCC2, forward 5′-GCT CCC GCA AAA ACT TGT GT- 3′, reverse 5′-CAT CGA CGT CCT TCC CAA A-3′, probe 5′-ACC CTG AGG TGA CAC CCC TGC G-3′. Relative gene expression quantification was calculated according to the comparative threshold cycle method ($2^{-\triangle\triangle Ct}$) using β-actin as an endogenous control and commercial RNA control (Stratagene, La Jolla, CA) as calibrator.

Statistical analysis

χ^2-test was used to compare IR among different genotypes. The Spearman correlation coefficient analysis was used to determine the correlation between IR and different mRNA expression. All analyses were performed with the SPSS software package, version 12(SPSS Inc., Chicago, IL, USA).

Results

HDRA

The in-vitro chemotherapy drug response as measured by IR varied among 49 patients. The IR ($\bar{x} \pm s$) of four anticancer drugs CDDP, BCNU, VCR and VM26 were 37.8 ± 2.6, 29.7 ± 3.1, 31.3 ± 2.7, and 40.7 ± 2.7, respectively. According to IR ≥50% considered as sensitive, more than half samples were resistant to the four tested agents (Table 1).

Genotyping and mRNA expression of ERCC1 and ERCC2

For the ERCC1 C8092A polymorphism in tumor samples, the frequencies of C/C and C/A genotypes were found in 26.5%, 73.5%, while A/A genotype was not found. In terms of polymorphism of ERCC2 Lys751Gln, wild genotype (A/A) was presented in 45 of 49 (91.8%) patients. However, heterozygous variant (A/C) and homozygous variant (C/C) were only determined in 3 (6.1%) and 1 (2.0%) respectively. Wild genotype (G/G) of Asp312Asn was found in 47 (95.9%) and heterozygous variant in two cases (4.1%). In five tumor cell lines, heterozygous variants (A/C) for the C8092A polymorphism and wild genotype (G/G) of Asp312Asn were presented in all cell lines. For polymorphism of ERCC2 Lys751Gln, heterozygous variant (A/C) was presented in T98G, SF767 and UW28; wild genotype (A/A) was present in MGR1 and MGR2. Homozygous variants of codon 312 of ERCC2 were not observed.

The relative expression of ERCC1 mRNA was ranged from 0.01 to 69.55, and of ERCC2 mRNA was ranged from 0.01 to 10.50. There was a significant association between ERCC1 and ERCC2 mRNA expression (Spearman $r = 0.42$, $P < 0.003$).

In vitro chemotherapy drug response and genotyping

Patients were classified into two groups based on HDRA results, ie IR ≥50% was responder and IR <50% was non-responder. The chemotherapy response of all four tested agents in wild genotype of ERCC1 and ERCC2 did not show a significant difference from that of the variant genotypes (Table 2). Age, sex, and histology did not affect response to chemotherapy drugs (data not shown).

Table 2 Comparison of chemotherapy drug response with different genotyping

	Genotype	Non-responder (%)	Responder (%)	*P*
CDDP				
ERCC1 C8092A	C/A	23 (67.6)	13(86.7)	
	C/C	11 (32.4)	2 (13.3)	0.165
ERCC2 Lys751Gln	A/A	32 (94.2)	13 (86.7)	
	A/C	1 (2.9)	2 (13.3)	
	C/C	1 (2.9)	0 (0.0)	0.310
ERCC2 Asp312Asn	G/G	32(94.1)	15 (100.0)	
	G/A	2 (5.9)	0 (0.0)	0.338
BCNU				
ERCC1 C8092A	C/A	30 (73.2)	6 (75.0)	
	C/C	11 (26.8)	2 (25.0)	0.915
ERCC2 Lys751Gln	A/A	38 (92.7)	7 (87.5)	
	A/C	2 (4.9)	1 (12.5)	
	C/C	1 (2.4)	0 (0.0)	0.850
ERCC2 Asp312Asn	G/G	39 (95.1)	8 (100.0)	
	G/A	2 (4.9)	0 (0.0)	0.542
VCR				
ERCC1 C8092A	C/A	31 (75.6)	5 (62.5)	
	C/C	10 (24.4)	3 (37.5)	0.442
ERCC2 Lys751Gln	A/A	38 (92.7)	7 (87.5)	
	A/C	2 (4.9)	1 (12.5)	
	C/C	1 (2.4)	0 (0.0)	0.850
ERCC2 Asp312Asn	G/G	40 (97.6)	7 (87.5)	
	G/A	1 (2.4)	1 (12.5)	0.188
VM26				
ERCC1 C8092A	C/A	24 (70.6)	12 (80.0)	
	C/C	10 (29.4)	3 (20.0)	0.492
ERCC2 Lys751Gln	A/A	32 (94.2)	13 (86.7)	
	A/C	1 (2.9)	2 (13.3)	
	C/C	1 (2.9)	0 (0.0)	0.310
ERCC2 Asp312Asn	G/G	32 (94.1)	15 (100.0)	
	G/A	2 (5.9)	0 (0.0)	0.338

In vitro chemotherapy drug response and mRNA expression

Spearman correlation coefficients between IR and mRNA expression of ERCC1, ERCC2 are displayed in Table 3. ERCC1 expression was reversely correlated with IR of CDDP, BCNU and VCR, while ERCC2 expression was reversely correlated with IR of BCNU. Especially, the very strong reverse correlations were appeared between ERCC1 and CDDP (Spearman

Table 3 Spearman correlation coefficients between IR and ERCC1, ERCC2 expression

IR	ERCC1	ERCC2
CDDP	–0.543 ($P = 0.0001$)	0.087 ($P = 0.277$)
BCNU	–0.270 ($P = 0.030$)	–0.373 ($P = 0.004$)
VCR	–0.289 ($P = 0.022$)	–0.041 ($P = 0.389$)
VM26	0.179 ($P = 0.109$)	–0.028 ($P = 0.425$)

r = –0.543) as well as ERCC2 and BCNU (Spearman r = –0.373).

Discussion

DNA repair systems are critical for repairing DNA damage induced by carcinogens. However, they also play an important role in repairing the cross-linking and oxidative damage caused by chemotherapy drugs [25]. Therefore, on the one hand, impaired DNA repair capacity may increase carcinogenesis and lead to more biologically aggressive tumors and decreased survival, on the other hand, decreased DNA repair due to weak DNA repair capacity may contribute to the persistence of functional platinum-DNA adducts that confer anti-tumor activity and impart more favorable prognoses.

It has been shown that ERCC1 and ERCC2 have pivotal roles in the NER pathway. ERCC1 and ERCC2 are separated by <250 kbp on chromosome 19q 13.2–13.3, suggesting a close link in DNA repair function. As for the influence of the ERCC1 polymorphism at C8092A located in the 3-untranslated region of the gene, one study in gliomas suggested that C8092A polymorphism affect ERCC1 mRNA stability and has been associated with the risk of adult-onset gliomas [18]. As for the influence of the ERCC2 polymorphism at codon 312 and 751 in the gliomas, it has been found that cases were less likely than controls to carry a variant nucleotide at each of the codons 312 and 751 [17]. To date, no study has examined the associated between ERCC1 and ERCC2 polymorphisms and chemotherapy drug response in the gliomas yet. Although several investigations have demonstrated that ERCC1 wild type (C/C) C8092T and ERCC2 Lys751Gln A/A genotype were important markers of improved patient survival [20, 26], in the present study no significant difference in chemotherapy drug response were observed either for ERCC1 or ERCC2 SNPs, perhaps due to the small number of patients included.

In the present study, a moderately strong correlation has been found between ERCC1 and ERCC2 gene expression levels and this result was in agreement with a previous report [14]. Experimental studies have demonstrated that increased ERCC1 levels were associated with removal of CDDP-induced strand adducts and relative CDDP resistance [5–7], as has been shown in the present study. In addition, ERCC1 defective knockout mice are highly sensitive to DNA cross-linking agents [27]. A positive correlation between ERCC1 mRNA levels in peripheral blood lymphocytes and DNA repair capacity has been reported [28, 29], indicating that ERCC1 mRNA levels can be used as a proxy when tissue is not available [14]. Meanwhile, we also found that ERCC1 mRNA expression was reversely correlated with BCNU and VCR sensitivities. This indicated that ERCC1 mRNA expression level was an important marker as drug cytotoxic response. In the present study, a reverse correlation was found between ERCC2 mRNA and BCNU cytotoxic response. This is a similar result as we previously found in the cell lines [10, 30, 31].

In conclusion, our present data indicated that ERCC1 mRNA level is associated with CDDP, BCNU and VCR cytotoxicity, while ERCC2 expression is associated with BCNU cytotoxicity in human gliomas. However, there was no association between ERCC1, ERCC2 SNP and chemotherapy drug response be found, at least in those tested drugs CDDP, BCNU, VCR and VM-26.

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