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Original Article

Correlation between SNPs of *XPD751*, *XPD312* and chemotherapeutic efficacy in colorectal carcinoma patients

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Abstract: Objective: To investigate the correlation between single nucleotide polymorphisms (SNPs) of *XPD751*, *XPD312* and the sensitivity of FOLFOX regimen in the patients with advanced colorectal cancer (CRC), and evaluate the SNPs of the two on the prognosis in advanced CRC. Methods: 88 patients were diagnosed as advanced CRC by CT scan. Blood routine, liver function and electrocardiogram (ECG) examinations were carried on before chemotherapy. The patients were with score of 1~2 according to Eastern Cooperative Oncology Group (ECOG). The blood sample was collected from each patient before treating with FLOFOX. All the 88 patients were treated with FLOFOX. Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) was used to detect the SNPs in *XPD751* and *XPD312*. The correlation between different genotypes and the prognosis of FOLFOX was analyzed. Results: ① In *XPD751*, there were 61 cases with Lys/Lys (69.3%), 55 as DRC (90.2%), while 27 cases with Lys/Gln + Gln/Gln (30.7%), 18 as DRC (66.7%). There was significant difference on chemotherapeutic efficacy between the two (X^2=5.601, P=0.037). In *XPD312*, there were 50 cases with Asp/Asp (56.8%), 33 as DRC (66.0%), while 38 cases with Asp/Asn + Asn/Asn (43.2%), 34 as DRC (89.5%). There was no significant difference on chemotherapeutic efficacy between the two (X^2=2.388, P=0.067). The sensitivity to FOLFOX in the patients with Lys/Lys was 2.8 times as those with Lys/Gln + Gln/Gln (OR=2.815, P<0.05. ② There was difference between the PFS in patients with Lys/Lys (9.85 months) and those with Lys/Gln + Gln/Gln (8.03 months), significantly (X^2=12.376, P<0.05). There was no significant difference between the PFS in the patients with Asp/Asp (10.04 months) and those with Asp/Asn + Asn/Asn (8.50 months) (X^2=13.690, P<0.05). ③ The PFS of the patients with Lys/Lys in *XPD751* combined with Asp/Asp in *XPD312* was 13.08 months, the patients with Lys/Lys combined with Asp/Asn + Asn/Asn was 8.60 months, the patients with Lys/Gln + Gln/Gln combined with Asp/Asp was 7.93 months, and the patients with Lys/Gln + Gln/Gln combined with Asp/Asn + Asn/Asn was 7.33 months. Comparing the PFS of the 4 mentioned above, there was significant difference (X^2=13.690, P<0.05). ④ COX regression analysis showed that in sex, age, metastasis and the 4 genotypes, only the *XPD751* Lys/Lys combined with *XPD312* Asp/Asp was related to PFS, significantly (P<0.05, RR=0.308). ⑥ The major adverse reaction presented as myelosuppression, without significant difference comparing the SNPs between in *XPD751* or in *XPD312*, including leukopenia or thrombocytopenia mainly in grade I or grade II, anemia mainly in grade I, nausea and vomiting mainly in grade II, liver injury mainly in grade I, peripheral nerve injury mainly in grade II. Conclusions: *XPD751* SNPs was the prognostic factor related to the sensitivity to FOLFOX in patients with advanced CRC, while *XPD312* SNPs was not. The patients with wile type of *XPD751* or *XPD312* were more sensitive to FOLFOX.

Keywords: Single nucleotide polymorphisms, colorectal cancer, FLOFOX, prognosis

Introduction

In the world, the incidence of the colorectal cancer (CRC) was at the second place [1] with 10~15% incidence in all tumor [2]. There was no significant characteristic in the early stage of CRC, while almost all the patients were diagnosed and confirmed as with CRC in the advanced stage, with losing the best treatment opportunity. In the patients with CRC, who received resection treatment, the average recurrence rate was 30~50% and the survival rate was 70% in 5 years. Therefore, chemotherapy was important in the treatment for the patients whoever already lost the treatment opportunity or receiving resection treatment [3]. Platinum-based chemotherapy was commonly used in the treatment of CRC pa-

tients, with the representativeness of oxaliplatin (L-OPH). However, with the same treating regimen and dosage, different patients were with different sensitivity during the treating process, even without effect.

As the development of human genome and pharmacogenetics, the association of DNA repair genes with the sensitivity of the patients to chemotherapeutic drugs, therapeutic effects and chemotherapy reaction draw more and more attentions. Therefore, the studies on the relative genes, as the targets of treatment and detection, in drug sensitivity and the prognosis in tumor therapy are needed further investigations.

L-OHP was the third commonly used medicine in platinum chemotherapy, which was with higher therapeutic effect and lower toxicity of chemotherapy, usually using in the monotherapy or combination regimen for CRC. Fujita et al. [4] L-OPH increased the efficiency and survival rate in the advanced CRC treatment but with larger individual differences and 20~40% influence of genetic factors. Many factors in chemical, physical or biological damages would induce DNA damage, including mutation, methylation, chromosome breakage and dimer. The DNA damage induced by these factors would be repaired by auto-DNA damage and repair system. Nowadays, there were 4 pathways in DNA damage repair including nucleotide-excision repair (NER), as the major one. Sarries et al. [5] considered that NER was one of the clear anti-tumor mechanisms by platinum drugs and the capacity of NER was related to the resistance of platinum drugs.

There was genetic diversity between individuals or populations, called single nucleotide polymorphism (SNP), which influenced the tumor susceptibility and resistances of chemotherapy drugs [6]. The product of Xeroderma pigmentosum group D (*XPD*), also known as excision repair cross-complementing group 2 (*ERCC2*), was one of the necessary helicases dependent on adenosine triphosphate (ATP) near the sites of DNA promoter and damage. The SNPs of XPD were related to the capacity of NER, influencing the transcription and translation of the proteins. The codons at *XPD751* and *XPD312* were sites with high mutational frequency, which were associated with the biomarkers of the patients with lung cancer in treatment with platinum drugs and the toxic reaction of chemotherapy [7]. However, there was no clear relationship between *XPD* SNPs and CRC, and the prognosis was still contradicted. Gan et al. [8] found that the patients with wild type XPD were with higher survival rate and better therapeutic effect.

FOLFOX regimen was proposed in the American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) guidelines, and related to the sensitivity to platinum drugs [9]. There was inconsistence about the effect of *XPD* SNPs on the prognosis of the FOLFOX treatment in advanced CRC patients. Therefore, the investigations on the correlation between the SNPs of *XPD751*, *XPD312* and the therapeutic effect of FOLFOX treatment in advanced CRC patients were important on clinical, which was helpful to the prognosis in the treatment with platinum drugs.

In our study, 88 patients were diagnosed as advanced CRC. The blood samples of the 88 patients were collected and the DNA was extracted. Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) was used to detect the SNPs of *XPD312* and *XPD751*. The association of XPD SNPs with FOLFOX regimen in treating patients with advanced CRC and the prognosis were analyzed.

Materials and methods

Patients

88 patients, 49 male and 39 female, age 27 to 77 with median age of 55, hospitalized at the oncology department one in the First Affiliated Hospital of Dalian Medical University from January 1st, 2009 to December 31st, 2013. There were 46 patients with colon cancer, 42 with rectal cancer, including 32 with liver metastasis, 11 with lung metastasis, 8 with liver combined with lung metastasis, 7 with pelvic metastasis, 27 with peritoneal metastasis, 3 with liver combined with supraclavicular lymph node metastasis. All the patients were diagnosed by CT scan and found the measuring lesions. Blood routine, liver function and electrocardiogram (ECG) examinations were carried on before chemotherapy with the Eastern Cooperative Oncology Group (ECOG) of 0~1. The generally clinical parameters of the 88 patients were shown in **Table 1**. Informed consents were obtained from all

Table 1. Clinical parameters of 88 patients with CRC

Parameters		Cases (n)	%
Sex	Male	49	55.7
	Female	39	44.3
Age	>60	40	45.5
	≤60	48	54.5
Metastatic sites	Liver	32	36.4
	Lung	11	12.5
	Liver and lung	8	9.1
	Pelvic	7	8.0
	Peritoneal	27	30.7
	Liver and supraclavicular lymph node	3	3.4
Differentiated degrees	High	12	13.6
	Moderate	50	56.8
	Mild	11	12.5
	Not obvious	15	17.0

Table 2. Primers of *XPD751* and *XPD312*

Gene	Primers	Size (bp)
XPD751	F: 5'-GCCCGCTCTGGATTATACG-3'	436
	R: 5'-CTATCATCTCCTGGCCCCC-3'	
XPD312	F: 5'-CTGTTGGTGGGTGCCCGTTATCTGTTGGTCT-3'	751
	R: 5'-TAATATCGGGGCTCACCCTGCAGCACTTCCT-3'	
β-actin	F: 5'-GCTCTGGCTCCTAGCACCAT-3'	75
	R: 5'-GCCACCGATCCACACAGAGT-3'	

Note: F: Forward primer; R: Reverse primer.

Table 3. PCR reaction system

	Volume (μl)
DNA template	10
Primers	F: 1
	R: 1
dNTP (1×)	4
TaqMan (1×)	0.25
PCR buffer (1×)	5
H_2O	28.75
Total	50

patients. The study involving the tissue samples was approved by the medical ethics committee of the First Affiliated Hospital of Dalian Medical University.

Genomic DNA extraction

2 ml of blood was collected from each patient before treating with FLOFOX. After anticoagulant treatment with sodium citrate (Solarbio technology Co., LTD, Beijing, China), the samples were stored in -20°C. The genomic DNA in the blood samples was extracted with genomic DNA extraction kit (Thermo Fisher Scientific, Inc. Shanghai, China).

PCR-RFLP

The SNPs in *XPD751* and *XPD312* were detected by PCR-RFLP. The primers were design by Invitrogen™ (Thermo). β-actin was taken as the internal parameter. The sequences were showed in **Table 2**. The PCR reaction system (50 μl) was showed in **Table 3**. The PCR reaction was carried on with the restriction enzymes of StyI and PstI under the conditions included predegeneration at 94°C for 3 min, degeneration at 94°C for 30 s, annealing at 55°C for 30 s, extension at 72°C for 30 s, totally 38 cycles and finally extension at 72°C for 10 min. The PCR products and the genotypes were analyzed by 1.5% agarose gel electrophoresis.

FOLFOX regimen

The 88 patients were received FOLFOX regimen as the treatment. 85 mg/m^2 L-OHP (Jiang Su Heng Rui Medicine Co., LTD, Lianyungang, China), day 1 (d1); 300 mg calcium folinate (CF, Jiang Su Heng Rui), d1~d2; 400 mg/m^2 5-fluorouracil (FU, Tianjing King York Amino Acids Co., LTD, Tianjing, China), d1~d2; 600 mg/m^2 5-FU was continuously infused for 48 h. Every 3-week was as a period. The patients were evaluated by CT scan after every 2 periods. At least 3 periods of treatment were completed for each patient. The average completed period was 4.

Therapeutic evaluation and indexes observation

The therapeutic evaluation was accorded to Response Evaluation Criteria in Solid Tumors (RESIST) Version 1.1, including 4 degrees as

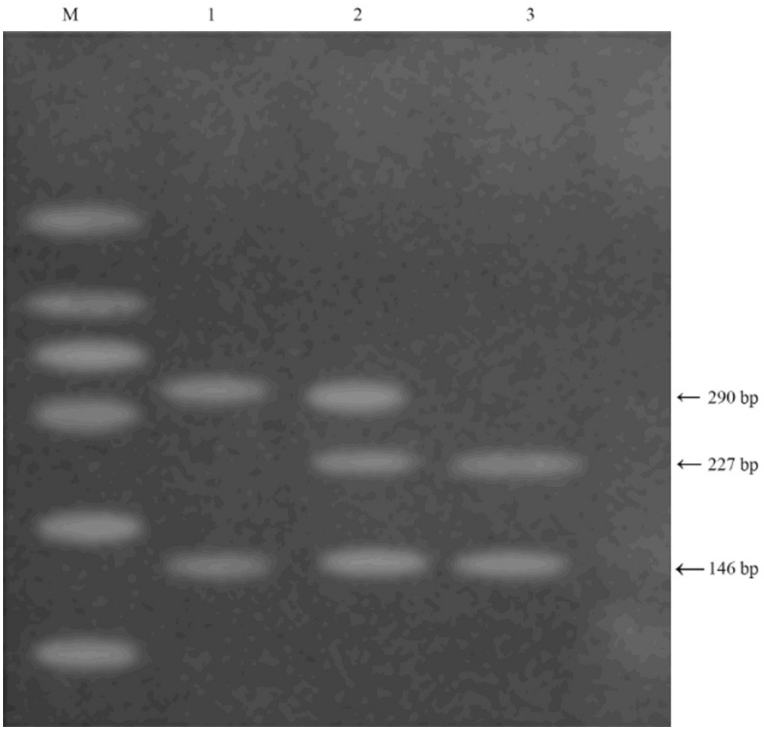

Figure 1. The fragments in *XPD312* after restriction enzyme analysis by StyI (M: DNA marker; Line 1: Asp/Asp 507 bp, 244 bp; Line 2: Asp/Asn 507 bp, 474 bp, 244 bp; Line 3: Asn/Asn 474 bp, 244 bp) (33 bp was not showed).

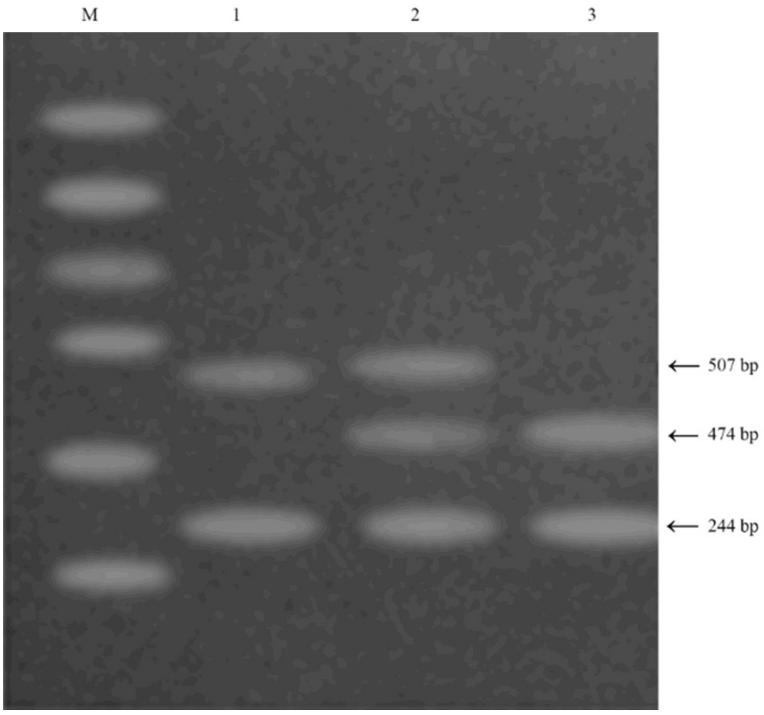

Figure 2. The fragments in *XPD751* after restriction enzyme analysis by PstI (M: DNA marker; Line 1: Lys/Lys 290 bp, 146 bp; Line 2: Lys/Glin 290 bp, 227 bp, 146 bp; Line 3: Gln/Gln 227 bp, 146 bp) (63 bp was not showed).

followed: complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). The patients were divided into CR group, PR group, SD group and PD group according to the evaluation. The observing indexes included disease control rate (DCR)=CR + PR + SD and progression-free survival (PFS) with following up until December 31st, 2013.

Statistical analysis

All the data were analyzed by SPSS 13.0 software. Chi-square test was used to compare the distribution differences among the groups. Fisher's exact test was used with the expected value less than 5. Logistic regression model was used to calculate the OR value and 95% confidence interval. Log-rank test was used to analyze the differences of PFS in different genotypes. COX regression was used to analyze the association of clinical parameters with genotypes. A value of $P<0.05$ considered significant difference.

Results

PCR products

StyI recognized the alleles of XPD312 with two restriction sites. There were 2 fragments including 507 bp and 244 bp after restriction enzyme analysis in Asp/Asp (wild type), 4 fragments including 507 bp, 474 bp, 244 bp and 33 bp in Asp/Asn (heterozygous mutant type), 3 fragments including 474 bp, 244 bp and 33 bp in Asn/Asn (homozygous mutant type) (**Figure 1**).

Table 4. Association of SNPs of *XPD751*, *XPD312* with chemotherapeutic efficacy

Genetype	CR	PR	SD	PD	N (frequency)	X^2	P
Lys/Lys	0	9	46	6	61 (69.3%)	5.601	<0.05
Lys/Gln + Gln/Gln	0	4	14	9	27 (30.7%)		
Asp/Asp	0	2	31	17	50 (56.8%)	2.388	0.067
Asp/Asn + Asn/Asn	0	5	29	4	38 (43.2%)		

Table 5. Logistic regression analysis on chemotherapeutic efficacy in the advanced CRC patients with Lys/Lys and Lys/Gln + Gln/Gln

Parameters	β	Wald	OR	95% CI	P
Sex	0.187	0.011	0.512	0.078~4.560	0.887
Age	0.136	3.428	1.803	0.499~6.105	<0.05
Metastasis	0.502	6.995	1.824	0.127~5.638	0.105
Genotype	1.770	3.983	2.851	0.897~15.404	<0.01

Table 6. Association of the genotype in *XPD312* and *XPD751* with PFS

Genotype	Median PFS	95% CI	P
Lys/Lys	9.85	6.839~14.071	<0.05
Lys/Gln + Gln/Gln	8.03	5.800~10.441	
Asp/Asp	10.04	8.903~11.052	0.231
Asp/Asn + Asn/Asn	8.50	7.682~10.209	

Table 7. COX regression analysis in the patients with different genotypes

Parameters	β	Wald	OR	95% CI	P
Sex	0.280	1.200	0.698	0.454~1.330	0.376
Age	0.301	1.117	1.289	0.810~2.105	0.398
Metastasis	0.010	0.038	1.012	1.005 ~1.138	0.985
Genotype	1.376	13.675	1.564	1.217~1.960	<0.01

PstI recognized the alleles of XPD751. There were 2 fragments including 290 bp and 146 bp in Lys/Lys (wild type), 4 fragments including 290 bp, 227 bp, 146 bp and 23 bp in Lys/Gln (heterozygous mutant type), 3 fragments including 227 bp, 146 bp and 63 bp (homozygous mutant type) (**Figure 2**).

Genotype of SNPs in XPD751 and XPD312

In XPD751 (exon 23), Lys mutated into Gln (A→C) and generated 3 types of SNPs including Lys/Lys (wild type), Lys/Gln (heterozygous mutant type) and Gln/Gln (homozygous mutant type). In XPD312 (exon 10), Asp mutated into Asn (G→A) and generated 3 types of SNPs including Asp/Asp, Asp/Asn (heterozygous mutant type) and Asn/Asn (homozygous mutant type).

Genotype of SNPs in XPD751 and XPD312 of CRC patients

The genotype frequency in XPD751 was calculated as 61 cases with Lys/Lys (69.3%), 15 cases with Lys/Gln (17.0%), 12 cases with Gln/Gln (13.6%). The genotype frequency in XPD312 was calculated as 50 cases with Asp/Asp (56.8%), 32 cases with Asp/Asn (36.4%), 6 cases with Asn/Asn (6.8%). Because there were fewer cases with homozygous mutant type, we compared the wild type with the heterozygous mutant type. There were 27 cases with Lys/Gln + Gln/Gln (30.7%) in XPD751, while 38 cases with Asp/Asn + Asn/Asn (43.2%) in XPD312.

Association of SNPs of XPD751, XPD312 with chemotherapeutic efficacy

In the cases with Lys/Lys, there were 9 cases evaluated as PR (14.8%), 46 as SD (75.4%), 6 as PD (9.8%), 55 as DRC (90.2%). In the cases with Lys/Gln + Gln/Gln, there were 4 cases evaluated as PR (14.8%), 14 as SD (51.9%), 9 as PD (33.3%), 18 as DRC (66.7%). There was significant difference between Lys/Lys and Lys/Gln + Gln/Gln (X^2=5.601, P=0.037, **Table 4**).

In the cases with Asp/Asp, there were 2 cases evaluated as PR (4.0%), 31 as SD (62.0%), 17 as PD (34.0%), 33 as DRC (66.0%). In the cases with Asp/Asn + Asn/Asn, there were 5 cases evaluated as PR (13.2%), 29 as SD (76.3%), 4 as PD (10.5), 34 as DRC (89.5%). There was no significant difference between Asp/Asp and Asp/Asn + Asn/Asn (X^2=2.388, P=0.067, **Table 4**).

The results of Logistic regression showed that the sensitivity to FOLFOX in the patients with Lys/Lys was 2.8 times as those with Lys/Gln + Gln/Gln (OR=2.815, P<0.05, **Table 5**).

Table 8. Association of *XPD751* and *XPD312* with adverse reaction (n=88)

Myelosuppression	Grade	Asp/Asp	Asp/Asn Asn/Asn	X^2	P	Lyn/Lyn	Lyn/Gln Gln/Gln	X^2	P
Leukopenia	≤II	40	29	0.077	0.754	48	21	0.054	0.469
	≥III	10	9			13	6		
Thrombocytopenia	≤II	45	30	1.036	0.622	54	22	1.088	0.435
	≥III	5	8			7	5		
Anemia	≤II	44	30	0.489	0.340	52	23	0.415	0.419
	≥III	6	8			9	4		
Nausea and vomiting	≤II	38	28	0.950	0.502	46	23	0.852	0.315
	≥III	12	10			15	4		
Liver injury	≤II	47	32	0.230	0.711	56	24	0.036	0.394
	≥III	3	6			5	3		
Peripheral nerve injury	≤II	43	30	1.832	0.103	55	23	1.256	0.102
	≥III	7	8			6	4		

Association of SNPs in XPD312 and XPD751 with PFS

In the 88 patients with advanced CRC, the median PFS was 9.97 months. The PFS in the patients with Lys/Lys was 9.85 months, while those with Lys/Gln + Gln/Gln were 8.03 months. There was significant difference between the two (X^2=12.376, P<0.05), indicating that the genotype of XPD751 was related to PFS. The PFS in the patients with Asp/Asp was 10.04 months, while those with Asp/Asn + Asn/Asn were 8.50 months. There was no significant difference between the two (**Table 6**).

The PFS of the patients with Lys/Lys in XPD751 combined with Asp/Asp in XPD312 was 13.08 months, the patients with Lys/Lys combined with Asp/Asn + Asn/Asn was 8.60 months, the patients with Lys/Gln + Gln/Gln combined with Asp/Asp was 7.93 months, and the patients with Lys/Gln + Gln/Gln combined with Asp/Asn + Asn/Asn was 7.33 months. Comparing the PFS of the 4 mentioned above, there was significant difference (X^2=13.690, P<0.05).

By COX regression analysis in the association of sex, age, metastasis and the 4 genotypes mentioned above with PFS, only the genotypes were related to PFS, significantly (P<0.05, RR=0.406). By analysis of the genotypes mentioned above, only the XPD751 Lys/Lys combined with XPD312 Asp/Asp was related to PFS (P=0.010, RR=0.308) (**Table 7**).

Association of XPD751 and XPD312 with adverse reaction in FOLFOX

The major adverse reaction in the 88 patients presented as myelosuppression. The patients with leukopenia or thrombocytopenia were most in grade I or grade II; those with anemia were most in grade I; those with nausea and vomiting were most in grade II; those with liver injury were most in grade I; those with peripheral nerve injury were most in grade II. There were no significant differences between the SNPs in XPD751 and XPD312. The data were showed in **Table 8**.

Discussion

In China, CRC was the malignance tumor with high incidence and mortality rate. FOLFOX and XELOX, basing on treatment combined with L-OPH, were identified as the effective treating regimens for CRC, which were helpful to improve the survival rate of the CRC patient. The treatments on advanced CRC and decreasing the recurrence rate were the important points in recent years.

Platinum drugs was common in treating CRC by binding to DNA and forming into platinum-DNA complex, which led to the formation of interstrand cross-linking with double-strand DNA and caused DNA damage. The DNA damage would activate the apoptosis and lead the cell to die. The DACH (1, 2-diaminocyelohexane) structure in L-OHP could bind to ornithine in the chain of DNA and form into DACH-Pt-DNA complex, which led to the cross-linking and damage in DNA, induced apoptosis in tumor cells and helpful for treatments.

FOLFOX, consisting of 5-FU, CF and L-OHP, was the common treating regimen used in CRC and with the correlation to SNPs.

DNA repair was the important pathway to maintain the stability of genetic information, which was influenced by SNPs. There were 4 pathways of DNA repair, including base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR) and double strand break repair (DSBR). The cell injury in human body induced by tumor was repaired by NER, which contained many proteins, such as XPA, XPB, XPC, XPD, XPE and XPG. Richard et al. [10] considered SPNs in XPD was related to the sensitivity and chemotherapy reaction in the chemotherapy with platinum.

Sitaram et al. [11] found that XPD participated in the process of DNA repair induced by N-m ethyl-N-n itrosourea (MNU), as one of the compositions of transcription factor II H (TF II H). The common SNPs in XPD included exons 6, 8, 10, 17, 22 and 23, whit the codons of 156, 199, 201, 312, 711 and 751. SNPs in XPD312 and XPD751, with the mutation of Asp→Asn and Lys→Gln, could change the amino acid (AA) and influence the activity of proteins [12].

XPD751 was considered to be related to the prognosis of chemotherapy in CRC. In the study on the correlation of treatment with 5-FU combined with L-OHP and the prognosis in CRC, Gan et al. [8] found that the mortality risk of the patients with XPD751 was 0.55 times than those with wile type, so they considered XPD SNPs was the evaluation index of the regimen of 5-FU combined with L-OHP. In the research on 72 patients who received FOLFOX6 regimen, Lamas et al. [13] detected the SNPs of XPD751, TS 5'-UTR, TS 3'-UTR, MTHFR C677T, A1298C, GSTP1 I105V, RECCI C118T and XRCC1 Arg399Gln in the blood samples by Snap and PCR technologies, then they found that only the genotype of XPD751 Lys/Gln was significantly related to PFS. In the results of Lamas et al. [13], the median PFS of Lys/Gln in XPD751 was 16 months (95% CI=9.2~22.7), Gln/Gln was 10 months (95% CI=6.1~13.9), and Lys/Lys was 8 months (95% CI=5.8~10.2), P=0.019. Analyzing GSTP1 combined with XPD751, the PFS of the patients with one or two favorable genotypes was 11 months (95% CI=7.4~14.6), while the one of those with unfavorable genotypes was 6 months (95% CI= 4.6~7.4), P<0.001. The risk of disease progression in XPD751 Lys/Lys was 1.93 (95% CI= 1.13~13.30, P=0.017), while in Gln/Gln was 2.1 (95% CI=1.01~4.22, P=0.047). Therefore, they considered XPD751 combined with GSTP1 was the factor of risk of disease progression in the patients who received FOLFOX6 regimen to treat metastatic colorectal cancer.

In our research, we studied on the 88 patients with advanced CRC, who received FOLFOX as the treatment. In the patients with Lys/Lys, the PFS was 9.85 months, which was longer than that in Lys/Gln + Gln/Gln (8.03 months), significantly (P<0.05). This result indicated that the sensitivity to FOLFOX of the patients with advanced CRC and XPD751 Lys/Lys was higher than that with Lys/Gln or Gln/Gln, which accorded to the results given by Lamas [13]. Therefore, XPD751 could be the prediction index in the patients with advanced CRC, who received FOLFOX as the treatment.

However, there were controversial problems about the association of XPD312 with the susceptibility of malignant tumor and the sensitivity to chemotherapy. On one hand, previous research [14] showed that XPD312 was the predictive factor of disease progression in the patients with metastatic CRC who received FOLFOX6. The susceptibility of the patients with XPD312 mutant genotype was 1.18 times of that in those with XPD312 wile type. Zeng et al. [15] considered that XPD312 mutant genotype could increase the risk of liver cancer, which also could be the predictive index of the susceptibility of acute leukemia [16]. On the other hand, in the research on Korean patients with CRC, Lee et al. [17] studied on the association of SNPs in ten genes, including XRCC1, TS, MTHFR, ERCC1, GSTT1, XPD, ABCC2, AGXT, GSTP1 and GSTM1, with the efficacy and toxicity of FOLFOX, and then they found that XPD genotypes were not related to the OS. Additionally, Tibaldi et al. [18] investigated on the association of efficacy of 65 patients with advanced nonsmall-cell lung cancer (NSCLC), who received gemcitabine combined with cisplatin regimen as the treatment, with SNPs in XPD312, and they found that there were no significant differences between XPD312 genotypes and the survival, time to progress (TTP) and OS.

In our study, the objective response rate (ORR) of the CRC patients with Asp/Asp was 4.0% (2/50), the disease control rate (DCR) was 66.0% (33/50), while in those with Asp/Asn +

Asn/Asn, the ORR was 13.2% (5/38), the DCR was 89.5% (34/38). These results indicated that there was no significant difference between XPD312 SNPs and the FOLFOX efficacy. The PFS of XPD312 Asp/Asp was 10.4 months, while Asp/Asn + Asn/Asn was 8.5 months, without significant difference. Therefore, we presumed that SNPs in XPD312 was no related to the survival of the patients with advanced CRC, who received FOLFOX as the treatment, which was consistent with previous researches [17, 18].

According to Kiyohara et al. [19], there was significant linkage disequilibrium in the SNPs between XPD751 and XPD312. In our study, we analyzed the patients with both wile type and/or heterozygote of XPD751 and/or XPD312, and the association of SNPs with PFS after FOLFOX. The results showed that there were significant differences among the four PFS as followed: the PFS of the patients with Lys/Lys in XPD751 combined with Asp/Asp in XPD312 (13.08 months), the patients with Lys/Lys combined with Asp/Asn + Asn/Asn (8.60 months), the patients with Lys/Gln + Gln/Gln combined with Asp/Asp (7.93 months), and the patients with Lys/Gln + Gln/Gln combined with Asp/Asn + Asn/Asn (7.33 months). However, analyzing the association of age, sex, genotypes and metastasis with PFS, only the genotypes were related to PFS, significantly ($P<0.05$, RR=0.406). Further analysis showed that only the XPD751 Lys/Lys combined with XPD312 Asp/Asp was related to PSF ($P=0.010$, RR=0.308). Therefore, we presumed that XPD751 Lys/Lys combined with XPD312 Asp/Asp was the prediction factor of advanced CRC. The patients with wild type of XPD751 and/or XPD312 were more sensitive to FOLFOX.

In the study on the association of toxicity of chemotherapy in treating lung cancer with XPD751 SNPs, Ding et al. [20] found that the reactions, including nausea, vomiting and alopecia, of the patients with XPD751 Lys/Lys were more serious than those with XPD751 Lys/Gln and Gln/Gln ($X^2=4.504$, $P=0.034$; $X^2=4.011$, $P=0.045$). However, in our study, there were no significant differences between XPD312 SNPs or XPD751 SNPs and the adverse reactions, presented as myelosuppression. This phenomenon might be considered about the tumor types, the living habits of the patients and the environment the patients living.

There were fewer researches on the difference of DNA repair capacity between the tumor cell and the normal cell depending on the peripheral blood samples. According to the research of Bosken et al. [21] basing on the peripheral blood samples, the DNA repair could influence the efficacy of chemotherapy, no matter in the tumor cell or the normal cell. So, the detection on the patients with advanced CRC but losing the operative chance by genomics was important, which was helpful to find the sensitivity of specific drugs.

Nowadays, the gene detection and the selection of suitable chemotherapeutic drugs draw more attentions in the individualized treatment of tumor all over the world. Because the chemosensitivity and the evaluation on the efficacy of chemotherapy were the complicated process with comprehension and multi-factor interactions, there were still controversies on the association of XPD SPNs with the efficacy of chemotherapy in the patients with advanced CRC. Firstly, there were multiple loci SNPs in XPD. Except for XPD751 and XPD312, the mutation of other sites also influenced the activity of relative proteins, leading to the differences of DNA repair capability. Secondly, the action process of platinum drugs, such as taking in and metabolism influenced the efficacy of chemotherapy.

To draw a conclusion, there still need further researches on the association of SNPs with chemotherapeutic efficacy, helpful for the selection of treating regimen by gene detection and prolonging the survival of the patients with advanced CRC.

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Disclosure of conflict of interest

None.

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