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ORIGINAL ARTICLE

Upregulated OCT3 has the potential to improve the survival of colorectal cancer patients treated with (m)FOLFOX6 adjuvant chemotherapy

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Abstract

Purpose To investigate the influence of organic cation transporter 3 (OCT3) expression on the effect of the combination regimen of 5-fluorouracil, folinic acid and oxaliplatin ((m)FOLFOX6) in colorectal cancer (CRC) patients.

Methods This is a retrospective study conducted at a single centre (Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital, China). Patients with stage IIb-IV resectable CRC who were being postoperatively treated with (m)FOLFOX6 as a first-line adjuvant chemotherapy regimen for at least 5 cycles and had resected primary tumour samples available were eligible for the study. Patients who preoperatively received chemotherapy and/or radiotherapy or were treated with targeted drugs or other anticancer drugs were excluded from the study. Immunohistochemical staining and digital image analysis were used to assess OCT3 expression in tumour samples. According to OCT3 expression level, the receiver operating characteristic curve (ROC curve) was used to divide the patients into two groups. Cox proportional risk regression was performed with the forward LR (forward stepwise regression based on maximum likelihood estimation) method using SPSS17.0 software. The primary endpoint was the 2-year progression-free survival.

Juan Gu and Dandan Dong are Co-first author

A brief description
This study explored the relationship of transporter OCT3 protein expression level in colorectal cancer tissues and the effect of oxaliplatin on colorectal cancer. The population we investigated were patients with stage IIb-IV resectable CRC who were postoperatively treated with (m)FOLFOX6 as a first-line adjuvant chemotherapy regimen. We found that the prognosis differed between patients with high OCT3 expression level and low OCT3 expression level, and the age of patients was negatively correlated with expression level of OCT3. These findings could help in implementing appropriate CRC treatment regimens.

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Results In total, 57 patients were included between 2014 and 2016 according to the inclusion and exclusion criteria (22 had low OCT3 expression, and 35 had high OCT3 expression). The mean age was 55.7 (30–74) years, and 37 of the total patients were male. According to TNM stage, 5 patients had stage IV disease, 44 patients had stage III disease, and 8 patients had stage II disease. Through Cox regression analysis, we found that among patients receiving the (m)FOLFOX6 regimen, those with higher OCT3 expression had a higher two-year progression-free survival rate than those with lower OCT3 expression ($P = 0.038$). The hazard ratio of patients with high OCT3 expression compared with patients with low OCT3 expression was 0.247. Besides, it was found that the age of patients was negatively correlated with expression level of OCT3, which can explain why patients over 70 years do not benefit from oxaliplatin-containing chemotherapy.
Conclusions High OCT3 expression in CRC tissues may be a protective factor for CRC patients treated with (m)FOLFOX6.

Keywords OCT3 · SLC22A3 · Colorectal cancer · (m)FOLFOX6 · Oxaliplatin

Introduction

Every year, colorectal cancer (CRC) kills almost 700,000 people, which makes it the fourth most deadly cancer worldwide following lung, liver and stomach cancer [1]. Oxaliplatin is a third-generation platinum anticancer drug widely used in cancer patients [2]. However, it is different from other platinum compounds, and among the platinum compounds approved for clinical application, only oxaliplatin has an antitumour effect on CRC. Unless contraindicated, oxaliplatin-based chemotherapy is the best choice for patients with stage III CRC [3]. Nevertheless, only approximately 50% of patients benefit from oxaliplatin [4]. Thus, it is necessary to explore how to improve the overall efficacy of oxaliplatin. To be effective, cytotoxic drugs must first cross the cell membrane to enter the cells [5]. The accumulation of platinum, including oxaliplatin, is decreased in resistant cells [6]. Currently, it is believed that the intake of platinum compounds is determined by passive diffusion, facilitated diffusion and active transport [7]. In the first few minutes after administration, passive diffusion is the main mechanism, and in later stages, protein-mediated transport predominates [8]. Although the ABC family plays a part in chemotherapeutic resistance by secreting anticancer drugs, the effect can be antagonized by specific intake transporters, and these transporters lead to beneficial higher drug concentrations, thus enhancing cancer cells chemosensitivity [9]. Therefore, intake transporters may be vital for the effect of oxaliplatin on CRC. Investigating intake transporters involved in oxaliplatin transport into CRC cells may facilitate improvements in the overall efficacy of oxaliplatin in CRC patients.

Organic cation transporters, which belong to the solute carrier 22 family, are responsible for transporting many endogenous small organic cations, drugs, and toxins. The expression of organic cation transporter 3 (OCT3) transporters in CRC cell lines is higher than that of OCT2 and other organic cation transporters, and the higher the expression of OCT3 in CRC cell lines is, the higher the concentration of oxaliplatin in the cells is [10]. Cisplatin and carboplatin, which are not transported by OCT3, are not effective for CRC treatment [7, 11]. Studies of the relationship between OCT3 and cancer have shown that OCT3 not only affects anti-tumour durg efficacy [12] but also may be involved in tumour development. It was reported that a common variant locus of SLC22A3 was significantly associated with distal colon cancer and appeared to contribute to increasing the CRC risk by approximately twofold [13], which indicated that OCT3 may play a role in the occurrence of colon cancer. Methylation of the promoter region of the *SLC22A3* (OCT3-encoding gene) in prostate cancer inhibits its expression [14], which is related to prostate cancer occurrence and development. Consequently, OCT3 may be a tumour suppressor gene in prostate cancer [15]. Additionally, results from the liver cancer model induced by diethylnitrosamine and phenobarbital indicated that tumour proliferation was significantly higher in OCT3-knockout mice than in wild-type mice, indicating that OCT3 deletion promoted the occurrence and proliferation of liver cancer [16]. Above all, OCT3 may play a protective role against CRC while enhancing the efficacy of oxaliplatin.

In this research, we retrospectively analysed the effect of OCT3 expression on the 2-year progression-free survival rate of CRC patients treated with the (m)FOLFOX6 regimen after CRC resection to investigate whether OCT3 expression level in CRC tissues can impact the effect of (m)FOLFOX6 regimen which containing oxaliplatin.

Materials and methods

Tissue samples and clinical data

This retrospective study was conducted at a single centre (Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital, China) and was approved by the ethics committees of the Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital in China. Written informed consent was not obtained from the patients or their relatives due to the retrospective study design using electronic health records, and no additional interventions were given to the subjects. We retrieved data between 2014 and

2016 from the Hospital Information System, and 57 patients were included in the analyses according to the inclusion and exclusion criteria. To exclude as much as possible other factors affecting OCT3 expression and prognosis of patients, patients with stage IIb-IV resectable CRC who were postoperatively treated with (m)FOLFOX6 as a first-line adjuvant chemotherapy regimen for at least 5 cycles and had available resected primary tumour samples were included in the study. Patients who were preoperatively treated with chemotherapy and/or radiotherapy or were treated with targeted drugs or other anticancer drugs were excluded from the study. Tumour samples came from paraffin sections of resected colon cancer from the Department of Pathology at the Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital. Patients were subjected to enhanced CT and enteroscopy, and blood tumour markers were measured once every six months to assess the state of recurrence or metastasis.

Immunohistochemical staining

The primary antibody used for immunohistochemistry was rabbit monoclonal anti-SLC22A3 (ab124826, 1:100; Abcam, USA). The 4-μm-thick tissue sections were incubated with the primary antibody overnight at 4 °C. Then, the tissues were incubated with a biotin-labelled goat anti-rabbit IgG polymer secondary antibody (SPlink Detection Kits from ZSGB-BIO, Beijing, China) at 37 °C for 30 min. Positive signals were visualized by microscopic observation after incubation with a DAB reagent kit (K135925C, ZSGB-BIO, Beijing, China) and incubation at room temperature for approximately 2 min. After counterstaining with haematoxylin, the slides were sealed with neutral balsam (20,160,508, Shanghai Yiyang Instrument Co., Ltd., Shanghai, China).

Virtual slice acquisition and imaging analysis

A BA200 Digital Trinocular Camera Microphotography System (Motic China Group Co., Ltd., Chengdu, China) was used to collect the images of the slices. A contour was first manually drawn to encircle an entire slice at low magnification (50X). Then, at high magnification (400X), three images were collected from three visual fields for each slice. An Image-Pro Plus 6.0 image analysis system (Media Cybernetics, USA) was used to measure the integrated optical density (IOD) and the area of all the images collected. The mean optical density (MOD) of three images from each sample was calculated.

Statistical analysis

A bilateral log-rank test was used to compare the progression-free survival rate of the two groups. A t test was used to compare quantitative data for two group, and a non-parametric Mann-Whitney U test was used for the enumeration of ranked data. The Pearson test was used for bivariate correlation analysis of quantitative data, and the Spearman test was used for the bivariate correlation analyses of ranked data. Statistical analysis was performed with SPSS17.0 software (IBM Corp, USA) and Graphpad Prism 5.0. Quantitative variables were expressed as the mean ± SEM. $P < 0.05$ was considered significant.

Results

Patient characteristics

A total of 57 patients with CRC were included between 2014 and 2016. The median follow-up time was 31 months. The mean cumulative dose of oxaliplatin was 682.7 mg/m^2, with a minimum of 417.0 mg/m^2 and a maximum of 1209.9 mg/m^2. Among the 57 patients, 37 were males, with an average age of 55.7 years, a youngest age of 30 years and an oldest age of 74 years. Among them, 14 patients had a family history of CRC or colon polyps. Thirty-four patients had rectal cancer, 8 patients had ascending colon cancer, 12 patients had descending colon cancer, 2 patients had transverse colon cancer, and 1 patient had total colon cancer. According to TNM stage, 5 patients had stage IV disease, 44 patients had stage III disease, and 8 patients had stage II disease. Twenty patients had poorly differentiated disease, and 37 patients had moderately differentiated disease. Twelve patients had peripheral nerve infiltration, and 45 patients had no peripheral nerve infiltration. The margin of all the surgical specimens was R0 (i.e., complete resection). Indicators that may affect prognosis, such as the expression of the tumour suppressor gene P53, vascular endothelial growth factor (VEGF), and the proliferation marker Ki67, chemotherapy cycles, cumulative oxaliplatin dose, and perineural invasion, are also listed in Table 1.

ROC curve for grouping according to OCT3 expression in CRC tissues

Representative images of immunohistochemical staining (400 x) for OCT3 in CRC patient tissues are shown in Fig. 1a. The ROC curve was constructed by selecting MOD of OCT3 as the test variable and the two-year progression-free survival (PFS) status of patients as the state variable. According to the cut-off value (0.3286) determined by the ROC curve, 57 patients were divided into either a low OCT3 expression group ($n = 22$) or a high OCT3 expression group ($n = 35$). The area under the ROC curve was 0.7 ($P < 0.05$), indicating that OCT3 expression may affect the two-year PFS rate associated with the (m)FOLFOX6 regimen (Fig. 1b).

Table 1 Characteristics of patients with CRC

Characteristics	No. of patients
Sex (male/female)	37/20
Median age, y (range)	55.7 (30–74)
Family history or polyps (yes/no)	14/43
Primary tumour site	
Ascending colon	8
Descending colon	12
Transverse colon	2
Rectum	34
Total colon	1
Histological status	
TNM stage: II	8
TNM stage: III	44
TNM stage: IV	5
Margin status	R0
Low differentiation	20
Intermediate differentiation	37
Other prognostic indicators	
P53:-	15
P53:+	6
P53:++	9
P53:+++	24
VEGF:-	9
VEGF:+	42
VEGF:++	3
Ki-67 mean (range)	0.50 (0.05–0.9)
Oxaliplatin-based chemotherapy cycles: mean (range)	7.1 (5–12)
5 cycles	8
6 cycles	18
>6 cycles	31
Cumulative dose of oxaliplatin (mg/m^2): mean (range)	682.7 (417.0–1209.9)
Perineural invasion (yes/no)	12/45
Two-year OS (survival/death/lost to follow-up)	46/6/5
Two-year PFS (survival/death/lost to follow-up)	39/13/5

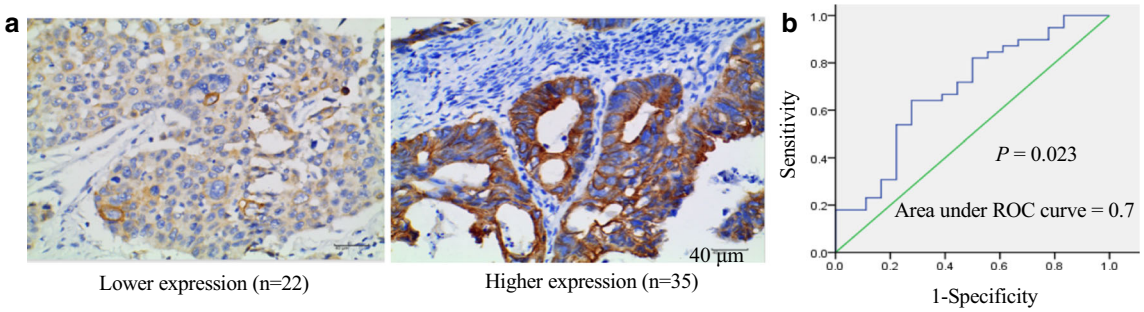


Fig. 1 Representative images of immunohistochemical staining and grouping by OCT3 expression in CRC patient tissues. (A: Tissues with low OCT3 expression stained light brown, while tissues with high OCT3 expression stained dark brown. B: Receiver operating characteristic (ROC) curve of the relationship between OCT3 expression and (m)FOLFOX6 response

Comparison of clinical parameters between OCT3 high and low expression groups

Differences in clinical parameters were compared between the high and low OCT3 expression groups. We found no significant differences in any of the clinical parameters between the two groups (Table 2). These results indicated that the two groups of patients had homogenous clinical characteristics.

Correlation analysis between OCT3 expression and clinical parameters

Pearson correlation analysis showed that OCT3 expression was negatively correlated with patient age at a level of 0.05. The older the patients were, the lower OCT3 expression was in cancer tissues. Pearson correlation analysis showed that OCT3 expression was positively correlated with the cancer marker alpha-fetoprotein (AFP). Spearman correlation analysis showed that the OCT3 expression was positively correlated with VEGF. No other parameters were found to be correlated with OCT3 expression (Table 3).

Univariate Kaplan-Meier analysis for factors affecting two-year PFS in patients treated with the (m)FOLFOX6 regimen

Univariate Kaplan-Meier analysis showed that peripheral nerve infiltration ($P = 0.002$) and tumour stage ($P = 0.001$) were significantly correlated with the two-year PFS in CRC patients treated with the (m)FOLFOX6 regimen. No other factors were found to be significantly associated with two-year PFS. OCT3 expression was not significantly correlated with the the two-year PFS rate of CRC patients treated with the (m)FOLFOX6 regimen ($P = 0.075$, <0.1) (supplement 1). Therefore, further proportional risk regression analysis was performed by selecting the peripheral nerve infiltration, tumour stage and OCT3 expression variables as covariates.

Table 2 Characteristics of patients with CRC stratified by OCT3 expression

Characteristics	Low OCT3 expression	High OCT3 expression	*P*
No. of patients	22 (38.6%)	35 (61.4%)	
Sex (male/female)	16/6	21/14	0.331
Mean age (range)	57.4 (30–73)	54.6 (37–74)	0.336
Family history or polyps (yes/no)	7/15	7/28	0.317
Primary tumour site			
Ascending colon	4	4	0.802
Descending colon	4	8	
Transverse colon	1	1	
Rectum	12	22	
Total colon	1	0	
Histological status			
TNM stage: II	2	6	0.902
TNM stage: III	19	25	
TNM stage: IV	1	4	
Margin status	R0	R0	
Low differentiation	7	14	0.684
Intermediate differentiation	15	22	
Other prognostic indicators			
P53: -	3	12	0.239
P53: +	2	4	
P53: ++	5	4	
P53: +++	10	14	
VEGF: -	5	4	0.095
VEGF: +	15	27	
VEGF: ++	0	3	
Ki-67 mean (range)	0.50 (0.05–0.9)	0.50 (0.1–0.9)	0.802
Oxaliplatin-based chemotherapy			
Number of cycles	6.64 (5–10)	7.57 (5–12)	0.088
Cumulative dose of oxaliplatin (mg/m^2)	625.7 (475.7–929.2)	718.5 (349.6–1209.9)	0.085
Perineural invasion (yes/no)	4/18	8/27	0.676

Table 3 Correlation analysis between OCT3 expression and clinical parameters

Parameters	r	*P*
Age	−0.319	0.016
Family history or polyps	−0.169	0.116
Primary tumour site	0.111	0.412
tumour stage	−0.115	0.394
Degree of tumour differentiation	−0.139	0.304
Perineural invasion	−0.026	0.847
Intraductal tumour thrombus	0.131	0.325
Microvessel density	0.024	0.862
AFP	0.283	0.033
CEA	−0.030	0.830
CA125	−0.097	0.542
CA19–9	0.044	0.760
CA50	−0.179	0.195
FER	−0.004	0.980
P53	−0.223	0.106
VEGF	0.319	0.019
Ki67	−0.115	0.408

Cox proportional risk regression for analysing factors affecting the two-year PFS in patients using the (m)FOLFOX6 regimen

The forward LR (forward stepwise regression based on maximum likelihood estimation) method was used. The above three variables that were identified as having a potential effect on the two-year PFS rate were included as covariates in Cox proportional hazard regression analyses. We found that high OCT3 expression was associated with a low death risk with a hazard ratio = 0.247 (95% CI 0.066–0.926) and $P = 0.038$ (Fig. 2), indicating that OCT3 expression is a protective factor for CRC patients treated with the (m)FOLFOX6 regimen. Besides, we also found TNM stage (hazard ratio = 8.791 [95% CI 1.593–48.529], $P = 0.013$) and perineural invasion (hazard ratio = 4.18 [95% CI 1.333–13.105], $P = 0.014$) was associated with a high death risk.

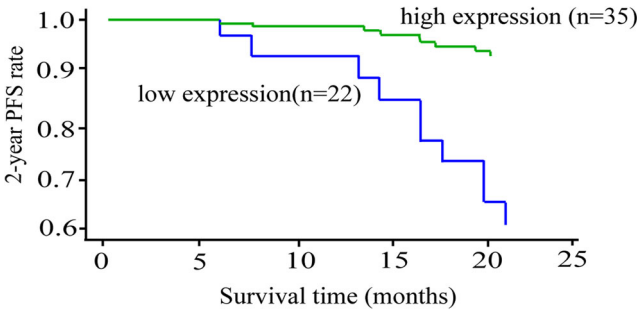


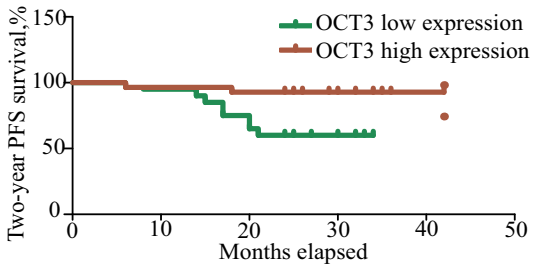
Fig. 2 Effect of OCT3 expression on the 2-year PFS of patients as determined by Cox regression analysis

Univariate Kaplan-Meier analysis to determine the effect of OCT3 on two-year PFS in patients with stage II or stage III CRC treated with the (m)FOLFOX6 regimen

We know that the death rate is significantly higher for patients with stage IV CRC than for other CRC patients. To remove the tumour stage bias, we analysed the effect of OCT3 expression on the two-year PFS of patients with stage II or stage III CRC by univariate Kaplan-Meier analysis. We found that the two-year PFS rates of high OCT3 expression group and low OCT3 expression group were 0.93 (95% CI 0.74–0.98) and 0.6 (95% CI 0.36–0.78) ($P = 0.007$), respectively, and the hazard ratio was 0.17 (95% CI 0.05–0.61) (Fig. 3), indicating that the death risk was lower in the OCT3 high expression group than in the OCT3 low expression group.

Discussion

In the present study, OCT3 expression in CRC tissues was positively correlated with the two-year PFS rate of patients treated with the oxaliplatin-based chemotherapy regimen (m)FOLFOX6. This finding may reveal a mechanism by which high OCT3 expression enhances the uptake of oxaliplatin into cancer cells [10, 11]. Moreover, that OCT3 itself inhibits cancer cells may be another explanation for this finding, and this is supported by studies demonstrating that OCT3 may be a tumour suppressor gene in prostate cancer [15], liver cancer [16] and familial oesophageal cancer as well as in further investigations showing that OCT3 inhibited cell motility by binding directly to ACTN4 and suppressing ACTN4-mediated actin crosslinking and filopodia formation [17, 18]. However, Le Roy et al. came to the opposite conclusion, finding that OCT3 expression was negatively correlated with the three-year recurrence-free survival of CRC patients treated with FOLFOX4. After analysing the major differences between our studies, we found that stage IV CRC patients were included in Le Roy's [19] research but not in ours. When CRC patients in stage IV were also included in our research, there was no significant difference between the two groups (not shown in this article). As we know, patients with stage IV CRC are patients who have distant metastases of cancer cells and their condition may be more complicated than that of patients without distant metastases. It is possible that the role of OCT3 is counteracted by other coexisting factors affecting the prognosis of patients with stage IV disease. In addition, research has shown that loss-of-function mutations in the BMPR2 gene contribute to marked medial hypertrophy in pulmonary arteries [20], a characteristic of advanced



No. at risk						
OCT3 high expression	28	28	27	12	6	0
OCT3 low expression	20	19	15	7	1	0

	Low expression (n=20)	High expression (n=52)	HR (95%)
Events	8	2	0.17 (0.05-0.6)
2-year PFS (95%CI)	0.6 (0.36-0.78)	0.93 (0.74-0.98)	

Fig. 3 Effect of OCT3 expression on the 2-year PFS of patients with stage II or stage III CRC as determined by univariate Kaplan-Meier analysis

idiopathic pulmonary arterial hypertension. Whether loss-of-function mutations exist in *SLC22A3* (the gene encoding OCT3) remains to be determined, but such mutations could result in high OCT3 expression but weak protein transport. This phenomenon could also lead to the differential conclusions drawn in the two studies. However, to date, there is no evidence to support this theory. The effect of OCT3 expression in CRC tissues on the prognosis of CRC patients treated with oxaliplatin-containing chemotherapy regimens may require further validation in larger sample studies. It is worth mentioning that the high OCT3 expression was positively correlated with the effect of oxaliplatin on colorectal cancer in vitro and in vivo experiments [21], which is consistent with the result of this clinical research.

Our results not only showed that OCT3 expression was positively correlated with the two-year PFS rate of CRC patients treated with oxaliplatin but also suggested that OCT3 expression in CRC tissues was negatively correlated with age, which could explain why patients over 70 years do not benefit from oxaliplatin-containing chemotherapy [22]. This suggests that older patients with CRC should be carefully considered when choosing oxaliplatin for chemotherapy. In China, patients with CRC are much younger [23], suggesting that the use of oxaliplatin may be applied to a larger population of patients. About OCT3 expression mechanism, some research suggested that OCT3 expression level is influenced by gene polymorphism and promoter region methylation of OCT3-encoding gene *SLC22A3* [14] that g.-81G > delA (rs60515630) and g.-2G > A (rs555754) of *SLC22A3* showed significant increases in OCT3 expression than the haplotypes that contained the major alleles. The high methylation of *SLC22A3* gene promoter region resulted in a decreased expression of OCT3. Whether hypermethylation of *SLC22A3* promoter region existed in elderly patients with colorectal cancer is worth further being investigated.

To preliminarily explore the protective mechanisms of OCT3 expression in CRC, we analysed the correlation between OCT3 expression and VEGF expression as well as serum tumour biomarkers, such as carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP) and cancer-related carbohydrate antigen (CA19–9, CA125, etc.). OCT3 expression was positively correlated with VEGF and AFP expression but not with other tumour markers. VEGF promotes angiogenesis. Moreover, it is widely believed that tumours cannot grow beyond 2 mm^3 without access to adequate oxygen and nutrients via vessels [24]. Therefore, VEGF is a factor that is beneficial for the growth of tumours. AFP, a glycoprotein belonging to the albumin family, is synthesized mainly by foetal hepatocytes and yolk sac cells and is essentially replaced by albumin 2–3 months after birth. It is closely related to the occurrence and development of a variety of tumours. It can inhibit the expression of the tumour suppressor gene phosphatase and tensin homologue deleted on chromosome ten (PTEN) and promote the occurrence of liver cancer [25]. As mentioned above, some studies have shown that OCT3 may be a tumour suppressor gene. Therefore, we intended to explore whether OCT3 expression might inhibit AFP and VEGF expression and thereby play a role in inhibiting tumours. However, we found a positive correlation between OCT3 expression and VEGF, and the same was true for OCT3 expression and AFP. We believe that upregulated OCT3 may be a compensation mechanism for the upregulation of VEGF expression to inhibit tumour growth. To clarify whether there exists a direct regulatory relationship between them, further studies are needed.

In brief, our findings suggest that OCT3 expression in CRC tissues is positively correlated with the two-year PFS rate of patients treated with (m)FOLFOX6, which indicates that increasing OCT3 expression could improve the prognosis of CRC patients. Moreover, OCT3 expression is negatively correlated with the age of patients. This study provides further supporting evidence for the choosing of chemotherapeutic medicines according to the age of CRC patients. The specific mechanisms by which high OCT3 expression could improve the prognosis of CRC patients as well as strategies to increase OCT3 expression still need to be explored.

Conclusion

The high OCT3 expression in CRC tissues may be a protective factor for CRC patients treated with (m)FOLFOX6 and (m)FOLFOX6 regimens especially may bring a better therapeutic effect for young CRC patients, the OCT3 expression of whose CRC tissues may present a high expression. Research included a larger sample size should be implemented to further confirm the conclusion. Gene polymorphysm and promoter region methylation of *SLC22A3* should be detected in order to explore the mechanism of influencing OCT3 expression.

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Author's contributions Conception and design: JG, LW, XJ. Acquisition of data: JG, EL, DD, Analysis and interpretation of data: JG, TL. Drafting the manuscript: JG, ST, SF. Final approval of the version to be published: JG, XJ. All authors read and approved the final manuscript.

Compliance with ethical standards

Ethics approval and consent to participate This study was approved by the ethics committees at Sichuan academy of medical Sciences & Sichuan Provincial People's Hospital in China. Written informed consent was not obtained from the patients or their relatives due to the retrospective study design of using the electronic health records and no additional interventions were given to the subjects.

Competing of interests The authors have no competing interests to declare.

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