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ORIGINAL PAPER

Overexpression of SGLT1 and EGFR in colorectal cancer showing a correlation with the prognosis

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Abstract Na+-dependent glucose cotransporter (SGLT1), reported overexpression in tumor tissues while its clinical significance was not established, and epidermal growth factor receptor (EGFR) with potential relation to SGLT1 were studied in order to investigate their clinical significance in colorectal cancer (CRC). Eighty-five patients of CRC who received chemotherapy in Sun Yat-sen Cancer Center from March 1st 2005 to December 31st 2008 were enrolled. SGLT1 and EGFR expression in these cancer tissues and 28 normal tissues were tested by immunohistochemistry. (1) Expression of SGLT1 ($P = 0.00$) and EGFR ($P = 0.01$) in cancer tissues was higher than that in normal tissues. (2) Their expression related with clinical stage ($P = 0.03$ and $P = 0.02$), but not with other clinical characteristics. (3) For first-line chemotherapy, expression of SGLT1 ($P = 0.06$ and $P = 0.21$) and EGFR ($P = 0.37$ and $P = 0.31$) had no influence on objective response rate (ORR) and disease control rate (DCR). EGFR overexpression was associated with lower disease-free survival ($P = 0.00$) and overall survival ($P = 0.01$), while SGLT1 did not ($P = 0.79$ and $P = 0.34$). *Conclusions* Both SGLT1 and EGFR overexpression in CRC was related to higher clinical stages. SGLT1 had a potential impact on the ORR of first-line chemotherapy in CRC. EGFR was associated with prognosis, while SGLT1 did not.

Keywords Colorectal neoplasms · SGLT1 · EGFR · Drug therapy · Treatment · Prognosis

Abbreviations

SGLT1	Na+-dependent glucose cotransporter
CRC	Colorectal cancer
ORR	Objective response rate
DCR	Disease control rate
EGFR	Epidermal growth factor receptor
PFS	Progression-free survival
OS	Overall survival

Introduction

Two categories of transporters are involved in glucose transport [1]: Na+-dependent glucose cotransporter (SGLT) including SGLT1, SGLT2, and SGLT3 and facilitative glucose transporters referred to as GLUT1-GLUT5. The former actively transports glucose depending on energy produced by Na+-K+ ATP pump, while the latter passively transports glucose along a glucose gradient. As the most primary active transporter, SGLT1 expression is affected by epidermal growth factor receptor (EGFR) [2]. EGFR, located in the cell surface, is a transmembrane glycoprotein composed of three parts: an extracellular binding domain, a hydrophobic transmembrane region spanning domain, and

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an intracellular tyrosine kinase domain [3]. Ligand binding to the extracellular domain activates cell proliferation, survival, angiogenesis, metastasis, and protects the cell from apoptosis [3]. In addition, it is reported in the journal *Cancer Cell* that extracellular domain of EGFR also interacts with SGLT1 [2].

SGLT1 plays an important role in maintaining enough glucose for cell survival since it is an active transporter for glucose. A recent study has demonstrated the level of SGLT1 protein and its transport activity are elevated in colon cell lines by a novel mechanism of EGFR independent of its tyrosine kinase activity [2]. Overexpression of EGFR is seen in 60–80% of patients with colon cancer [4], providing the basis for exploiting the EGFR signaling pathway as a therapeutic target in the treatment of this group of cancers. The protein level of EGFR decreases after cell lines transiently transfected with EGFR siRNA and so does SGLT1 protein level and intracellular glucose level, which in turn induce cell death because of low energy [2].

This study planned to test the expression of EGFR and SGLT1 in CRC, to assess the correlations of EGFR expression and SGLT1 expression and some clinical characteristics, and furthermore, to evaluate the significance of EGFR and SGLT1 expression predicting efficacy and prognosis.

Patients and methods

Patients

The criteria of patients' selection: (1) CRC with definitive pathological diagnosis; (2) Received standard first-line chemotherapy in Sun Yat-sen Cancer Center from March 1st 2005 to December 31st 2008; (3) With complete clinical and pathological information. The initial plan was to select randomly 100 patients with CRC from the bank of CRC cases in our hospital. Ultimately, 85 cases were entered in this study since 15 patients were unavailable for paraffin-embedded specimens block. Surgical margins of 28 cases were available in above-mentioned 85 patients and those were used as control group of colorectal normal tissues.

Methods

Immunohistochemical staining: The formalin fixed, paraffin-embedded pathology specimens of 85 CRC tissues and 28 colorectal normal tissues were examined. It was confirmed microscopically that all specimens of hematoxylin and eosin staining contained cancer by a pathologist. Sections of 5-μm-thick cut from paraffin block were put on glass slides. The slides were dried in the incubator at 60°C, deparaffinized in xylene, and then rehydrated in a downgraded series of ethanol. After flushing in water, antigen retrieval with citrate buffer was performed under high temperature and high pressure conditions. The sections cooled down for 20 min, flushed in PBS twice for 5 min, and then incubated in serum for 10 min. The primary antibody (SGLT1 from Abcam, USA; EGFR from Cell Signal, USA), 1/50 diluted in 1% PBS, was incubated for 45 min after tipping serum, and then the anti-rabbit secondary antibody (from Invitrogen, USA) was incubated for 30 min after flushed in PBS twice for 5 min. Diaminobenzidine (DAB, from Invitrogen, USA) was used for 10 min to visualize immunolabeling after flushed in PBS twice for 5 min. After washing, the sections were counterstained with hematoxylin (from Invitrogen, USA). Intestinal and laryngeal tissue was used as a positive control for SGLT1 and EGFR, respectively. PBS was used as negative control instead of the primary antibody on each slide for both of SGLT1 and EGFR.

Histological score (Hscore) assessment: Two independent pathologists with no knowledge about clinical data scored all immunohistochemical stainings of SGLT1, EGFR according to staining intensity and the percentage of positive staining tumor cells. Staining intensities were classified by 5 grades for SGLT1: from 0 (no staining), 1 (pale yellow), 2 (yellow), 3 (deep yellow) to 4 (brown); 4 grades for EGFR from 0 (pale yellow or no staining), 1 (yellow), 2 (deep yellow) to 3 (brown). The percentage of tumor cells staining positive was scored in 6 grades for SGLT1: from 0 (0%), 1 (0–20%), 2 (20–40%), 3 (40–60%), 4 (60–80%) to 5 (80–100%); 4 grades for EGFR: from 0 (0–10%), 1 (10–25%), 2 (25–50%), 3 (50–100%). Intensity and percentage of positive staining tumor cells was scored after counting at least 10 high power fields, final magnification 10 × 40. Mean Hscores were calculated as follows: [(Intensity reader 1 × Percentage reader 1) + (Intensity reader 2 × Percentage reader 2)]/2.

Statistical analysis

All statistics were calculated using SPSS for Windows, version 17.0. Nonparametric tests were used to compare the expression of SGLT1 and EGFR between two groups that every clinicopathological characteristic dichotomized. Correlations of EGFR Hscores and SGLT1 Hscores were assessed by Spearman's correlation analysis. Chi-square test was used to analyze the objective response rate (ORR) and disease control rate (DCR) of first-line chemotherapy among different level expression of SGLT1 and EGFR. Kaplan–Meier curves and Cox regression model were used as univariate analysis and multivariate analysis to evaluate progression-free survival (PFS) and overall survival (OS). Significance was defined as $P \leq 0.05$. All P values were two sided.

PFS was calculated from the date of chemotherapy until to the time of relapse or progressive disease. Patients with no signs of relapse were censored at the time of last

follow-up or death. Overall survival was calculated from the day of diagnosis until death or last follow-up.

Results

The baseline characteristics of the 85 patients with CRC were listed in Table 1. The median follow-up was 34.0 months (2. 0 $\sim$ 137.0 months). At the end of follow-up time of May 1st 2010, there were 51 patients dead and 33 patients alive (26 patients with PS $\leq$ 1, 4 patients with PS = 2, 3 patients with PS = 3). One patient lost follow-up.

Expression of SGLT1 and EGFR in CRC tissues and normal tissues

All the 85 CRC tissues and 28 normal colorectal tissues were successfully tested for the **e**xpression of SGLT1 and EGFR. Hscore was categorized into 11 grades for SGLT1 and 8 grades for EGFR. The positive expression rate of SGLT1 was 55.3 and 7.2% in cancer tissues and normal colorectal tissues, while that of EGFR was 44.7 and 21.4%, respectively, as shown in Fig. 1. Table 2 displayed statistically different expression of SGLT1 and EGFR in cancers and normal tissues. Expression of both SGLT ($P = 0.00$) and EGFR ($P = 0.01$) in cancers was higher than that in normal tissues.

Relationship among EGFR expression, SGLT1 expression, and clinical characteristics of CRC

In order to analyze the clinical significance of EGFR and SGLT1 expression in CRC, the association between the expression of EGFR and SGLT1 and clinical characteristics including: gender, age (at risk group or not), family history of

Table 1 Clinicopathological characteristics of 85 cases with CRC and the expression of EGFR and SGLT1 in the subgroup

Clinical factor	No. (%)	SGLT1 expression (No.)				EGFR expression (No.)			
		Low	Moderate	High	*P* value	Low	Moderate	High	*P* value
Gender									
Male	54 (63.5)	24	15	15	0.78	30	12	12	0.95
Female	31 (36.5)	14	10	7		17	7	7	
Age									
Median	50								
Range	12–79								
Risk group (40–59 years)	46 (54.1)	21	10	15	0.57	25	8	13	0.52
Nonrisk group (<40 years or >60 years)	39 (45.9)	17	15	7		22	11	6	
Family history									
Yes	12 (14.1)	2	6	4	0.08	7	3	2	0.73
No	73 (85.9)	36	19	18		40	16	17	
Tumor site									
Rectum	24 (28.2)	12	8	4	0.34	13	5	6	0.82
Colon	61 (71.8)	26	17	18		34	14	13	
Primary clinical stage									
II	12 (14.1)	7	3	2	0.03	9	2	1	0.02
III	25 (29.4)	15	5	5		17	4	4	
IV	48 (56.5)	16	17	15		21	13	14	
Histological differentiation									
Well differentiation	6 (7.1)	5	1	0	0.68	4	1	1	0.51
Media differentiation	57 (67.1)	21	21	15		32	13	12	
Poor differentiation	22 (25.9)	12	3	7		11	5	6	

The table shown baseline clinicopathological characteristics of the 85 patients with CRC. Different expression of EGFR and SGLT1 between two groups, that every clinicopathological characteristic dichotomized, was compared by nonparametric test with *P* value listed

Histological type was not listed because all cases were adenocarcinomas

Different expression of SGLT1 and EGFR was analyzed statistically in different clinical stage by II united with III versus IV because the number of stage II was small. In addition, no stage I was available in the study

Different expression of SGLT1 and EGFR was analyzed statistically in different histological differentiation by well united with media versus poor because the number of well differentiation was small

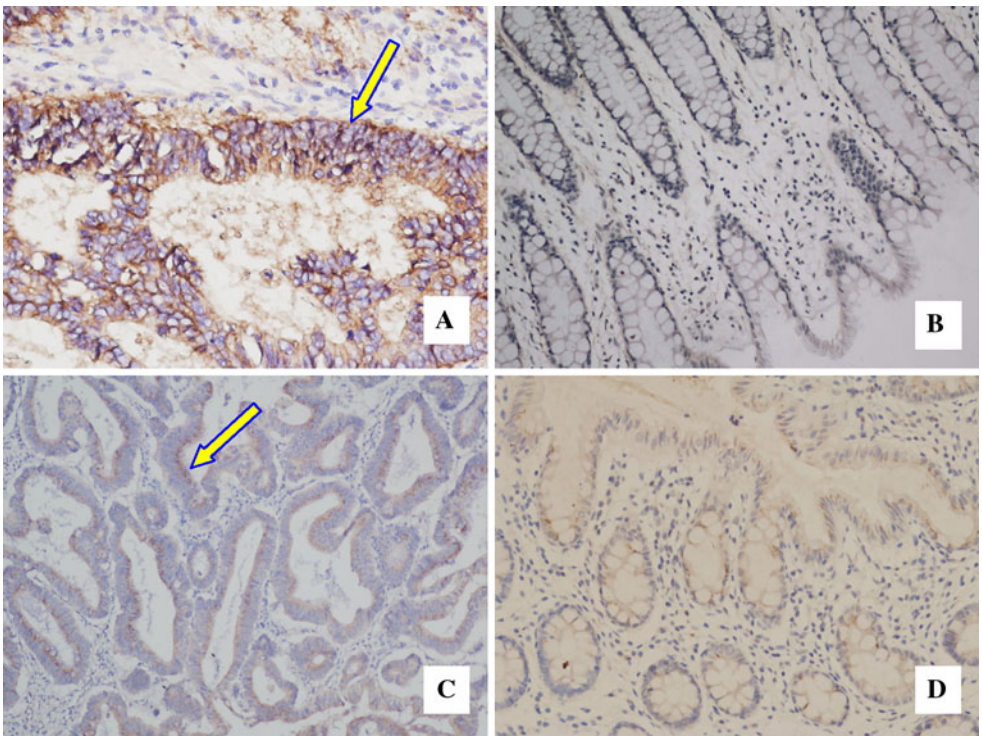

Fig. 1 Immunohistochemistry photomicrographs (200×): EGFR displayed strongest membranous staining in CRC tissues (*arrow*) and absent in normal tissues, as showed in photographs **a**, **b**. SGLT1 displayed intense granular staining of the cytoplasm in CRC tissues (*arrow*) and absent in normal tissues, as showed in photographs **c**, **d**

Table 2 Expression of EGFR and SGLT1 in CRC and colorectal normal tissues

	CRC tissues No. (%)			Colorectal normal tissues No. (%)			Mean Hscore (range)		
	Low	Moderate	High	Low	Moderate	High	Cancer	Normal	*P*
SGLT1 expression	38 (44.7%)	25 (29.4%)	22 (25.9%)	26 (92.9%)	1 (3.6%)	1 (3.6%)	3.04 (0–20.0)	0.11 (0–2.0)	0.00
EGFR expression	47 (55.3%)	19 (22.4%)	19 (22.4%)	22 (78.6%)	6 (21.4%)	0 (0.0%)	2.12 (0–9.0)	0.25 (0–2.0)	0.01

Expression of EGFR and SGLT1 in CRC and colorectal normal tissues was categorized into 3 grades and the cases at every grade were listed: a low expression defined as Hscore = 0, a moderate expression defined as Hscore ≤ 4.0, and a high expression defined as Hscore > 4.0. Nonparametric test was used to compare the different expression of SGLT1 and EGFR between CRC tissues and normal tissues with *P* value listed

cancers, primary tumor site (colon or rectum), clinical stage, and histological differentiation was calculated by Nonparametric test. As shown in Table 1, the expression level of SGLT1 ($P = 0.03$) and EGFR ($P = 0.02$) had significant correlation with the clinical stage, but not with other clinicopathological characteristics. In addition, no correlation between the SGLT1 and EGFR expression was found by Spearman's correlation analysis, $P = 0.67$.

Association of SGLT1 and EGFR expression with the effects of first-line chemotherapy and prognosis in CRC

Chi-square test was used to analyze the difference of ORR and DCR in low, median, and high expression of SGLT1 and EGFR, as shown in Table 3. Although SGLT1 ($P = 0.06$) and EGFR ($P = 0.37$) expression had no influence on ORR, a trend was found for SGLT1. Neither SGLT1 ($P = 0.21$) nor EGFR ($P = 0.31$) expression had effect on DCR.

Median PFS in the whole study cohort was 7.0 months. By univariate analysis (log rank test, Kaplan–Meier), EGFR Hscore was a predictive factor for PFS ($P = 0.00$) as shown in Fig. 2, while the following factors did not influence PFS: gender ($P = 0.65$), age ($P = 0.74$), family history of cancers ($P = 0.78$), primary tumor site ($P = 0.66$), clinical stage ($P = 0.52$), histological differentiation ($P = 0.48$), SGLT1 Hscore ($P = 0.79$). The median PFS was 7.0, 7.5, and 4.0 months in patients with low, median, and high SGLT1 expression, respectively. The median PFS was

Table 3 SGLT1 and EGFR expression effect on the ORR and DCR of first-line chemotherapy

		SGLT1 expression No. (%)			EGFR expression No. (%)		
		Low	Moderate	High	Low	Moderate	High
Objective response	No	23 (60.5%)	11 (44.0%)	17 (77.3%)	31 (66.0%)	9 (47.4%)	11 (57.9%)
	Yes	15 (39.5%)	14 (56.0%)	5 (22.7%)	16 (34.0%)	10 (52.6%)	8 (42.1%)
P		0.06			0.37		
Disease control	No	11 (28.9%)	3 (12.0%)	7 (31.8%)	11 (23.4%)	3 (15.8%)	7 (36.8%)
	Yes	27 (71.1%)	22 (88.0%)	15 (68.2%)	36 (76.6%)	16 (84.2%)	12 (63.2%)
P		0.21			0.31		

ORR and DCR cases of first-line chemotherapy were listed in the groups with different expression of EGFR and SGLT1. Expression of EGFR and SGLT1 was categorized into 3 grades: a low expression defined as Hscore = 0, a moderate expression defined as Hscore $\leq$ 4.0, and a high expression defined as Hscore > 4.0. Chi-square test was used to analyze different ORR and DCR of first-line chemotherapy in different groups with *P* value listed

8.0 months, 8.0 months, and 3.0 months in patients with low, median, and high EGFR expression, respectively. As potential predictors of PFS, all of aforementioned variables were enrolled in a multivariate model (Cox regression). As shown in Table 4, only EGFR Hscore showed its prognostic value, $P = 0.01$.

Median OS in the whole study cohort was 34.0 months. By univariate analysis (log rank test, Kaplan–Meier), EGFR Hscore ($P = 0.01$), clinical stage ($P = 0.00$), and histological differentiation ($P = 0.04$) were predictive factors of OS, which were shown in Fig. 3a–c. However, other factors including gender ($P = 0.62$), age ($P = 0.76$), family history of cancers ($P = 0.97$), primary tumor site ($P = 0.91$), and SGLT1 Hscore ($P = 0.34$) showed insignificant influences on OS. When the aforementioned variables were included in the multivariate analysis, only 2 predictive factors retained their prognostic value: TNM stage ($P = 0.01$) and EGFR Hscore ($P = 0.03$), as shown in Table 4.

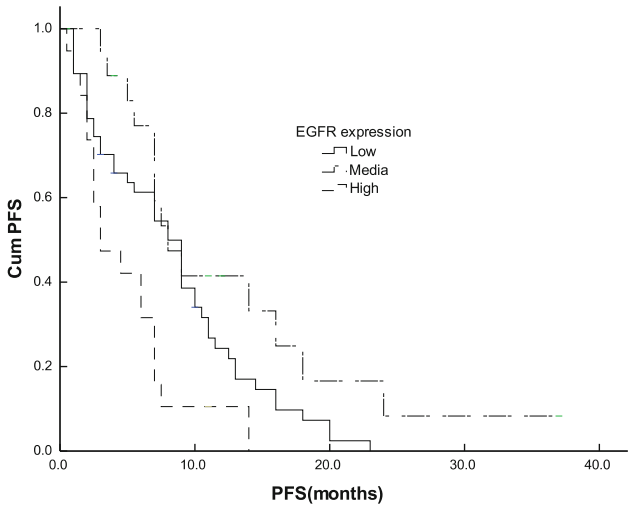

Fig. 2 Effect of EGFR expression on PFS (progression-free survival) in CRC. The Kaplan–Meier method was used to draw PFS curves, and different groups (three groups according to EGFR immunohistochemistry scores)were compared with the log rank test, $P = 0.00$

Discussion

Expression of SGLT1 and its clinical significance in CRC

The expression of SGLT1 is restricted to intestinal, renal epithelial cells, and endothelial cells lining the blood–brain barrier under physiological condition. To our knowledge, the present study was the first study to investigate the expression of SGLT1 in CRC. And we really found that SGLT1 expression in CRC tissues was significantly higher than that in normal colorectal tissues and expression rates were 55.3 and 7.2%, respectively. The high expression rate of SGLT1 in tumor tissues is possibly due to the cancer cells needing more glucose to provide energy. However, our findings were not accordant to the results reported in the studies about other cancers [5, 6]. In lung cancer, SGLT1 expression tested by RT–PCR had no difference among primary lung tumor, metastases, and normal tissue [5]. In pancreatic cancer, SGLT1 expression tested by immunohistochemistry also showed no difference between normal and cancer tissues [6]. Perhaps the different distributions of SGLT1 in different tissues contributed to the heterogeneity of expression of SGLT1 in different cancers. In addition, we found that SGLT1 expression correlated with the clinical stage ($P = 0.03$); the higher the clinical stage, the higher the level of SGLT1 expression. Based on our finding, it may implicate that the SGLT1 may play a key role, even participate in the carcinogenesis and development, in CRC. As a predictor of efficacy of CRC, the expression of SGLT1 showed a potential correlation with ORR ($P = 0.06$) of first-line chemotherapy, while it failed to predict the DCR, PFS, and OS. Based on the

Table 4 Multivariate analysis for PFS and OS of 85 patients with CRC

	PFS				OS			
	P	Exp (B)	95.0% CI for Exp (B)		*P*	Exp (B)	95.0% CI for Exp (B)	
			Lower	Upper			Lower	Upper
Gender	0.39	0.78	0.44	1.38	0.32	0.70	0.34	1.43
Age	0.42	1.25	0.72	2.17	0.55	0.82	0.43	1.57
Family history	0.86	1.06	0.54	2.08	0.81	0.91	0.41	1.99
Tumor site (colon/rectum)	0.26	0.72	0.40	1.28	0.81	1.09	0.52	2.30
Primary clinical stage	0.16	0.76	0.52	1.12	0.01	2.06	1.20	3.55
Histological differentiation	0.52	1.15	0.75	1.79	0.27	1.40	0.77	2.56
EGFR Hscore	0.01	1.11	1.02	1.21	0.03	1.12	1.01	1.24
SGLT1 Hscore	0.66	0.99	0.94	1.04	0.55	0.98	0.91	1.05

Cox regression model was used as multivariate analysis to evaluate PFS and OS with *P* and Exp (B) value listed in 85 cases with CRC. PFS was calculated from the date of chemotherapy till to the time of relapse or progressive disease. Patients with no signs of relapse were censored at the time of last follow-up or death. Overall survival was calculated from the day of diagnosis until death or last follow-up

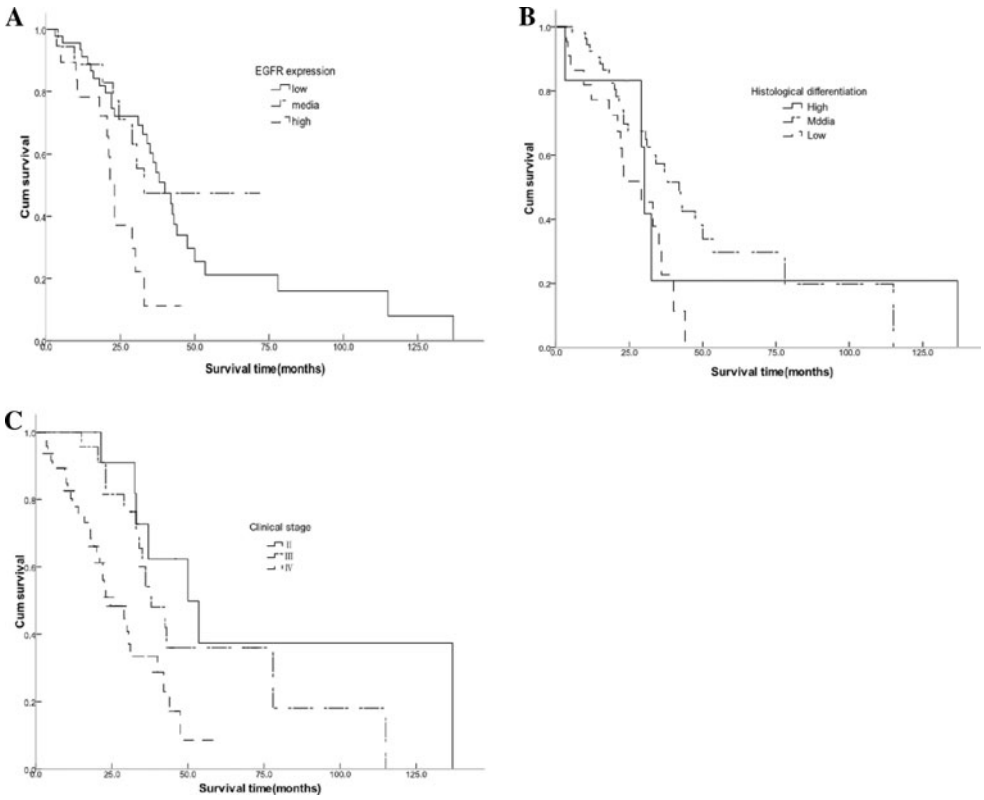

Fig. 3 Effect of EGFR expression, histological differentiation, and clinical stage on overall survival in CRC. The Kaplan–Meier method was used to draw survival curves, and different groups were compared with the log rank test. **a** Overall survival curves for low, median, and high EGFR expression, $P = 0.01$. **b** Overall survival curves for II, III, and IV clinical stage, $P = 0.00$. **c** Overall survival curves for high, median, and low histological differentiation, $P = 0.04$

above results, it maybe significant to test SGLT1 expression in CRC, but of course, more intensive studies on SGLT1 in CRC should be further conducted.

Expression of RGFR and its clinical significance in CRC

Different from SGLT1, the expression of EGFR was fully studied in most cancers [7]. However, the expression rates of EGFR in CRC were apparently different, ranging widely from 21 to 80% [4, 8, 9]. The present study demonstrated that the expression of EGFR was distinctively higher in colorectal cancer than that in normal colorectal tissue and the expression rates were 44.7 and 21.4%, respectively. A domestic study [9] found that positive expression of EGFR in colon cancer was higher than that in peritumoral tissues (43.10 vs. 7.14%, $P < 0.01$) and its obvious correlation with clinical stage, which agreed well with our study.

Based on the results of our study, the higher expression of EGFR in cancer tissue ($P = 0.03$) and its overexpression correlation with advanced clinical stage ($P = 0.02$), we inferred that EGFR played an important role in the carcinogenesis and development of CRC. In the present study, the EGFR expression was demonstrated as a predictor for OS and PFS of first-line chemotherapy in both univariate analysis and multivariate analysis. This suggested that the expression of EGFR, like TNM stage, was an independent prognostic factor in CRC. However, Spano et al. [10] found EGFR overexpression in 80% of cases and it was correlated with TNM stage, but with no survival correlation in 150 patients with CRC. In general, most researchers [11–13] considered higher EGFR expression associated with advanced clinical stage and shorter OS, which accorded with our results.

Relationship of SGLT1 and EGFR in CRC

A recent study [2] has demonstrated the levels of SGLT1 protein and its transport activity vary with changes of the levels of EGFR protein. When EGFR is blocked by EGFR siRNA, SGLT1 protein degradation increased and the expression of SGLT1 decreased. The outcome of SGLT1 protein degradation caused autophagic cell death in the cell. We can infer that EGFR expression is very important to keep SGLT1 stable. However, the present study failed to find the correlation of SGLT1 and EGFR protein expression in CRC tissue that maybe associated with the different conditions between colon cancer cell lines in others studies [2] and CRC tissue in our study. Certainly, more studies with a large patient sample are necessary to clarify the relationship of EGFR and SGLT1 in CRC tissue.

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References

1. Wood IS, Trayhurn P. Glucose transporters (GLUT and SGLT): expanded families of sugar transport proteins. Br J Nutr. 2003;89:3–9.
2. Weihua Z, et al. Survival of cancer cells is maintained by EGFR independent of its kinase activity. Cancer Cell. 2008;13:385–93.
3. Macarulla T, Casado E, Ramos FJ, Valverde C, Tabernero J. Epidermal growth factor receptor (EGFR) inhibitors in gastrointestinal cancer. Onkologie. 2006;29:99–105.
4. Dei Tos AP. The biology of epidermal growth factor receptor and its value as a prognostic/predictive factor. Int J Biol Markers. 2007;22(Suppl 4):S3–9.
5. Ishikawa N, Oguri T, Isobe T, Fujitaka K, Kohno N. SGLT gene expression in primary lung cancers and their metastatic lesions. Jpn J Cancer Res. 2001;92:874–9.
6. Casneuf VF, et al. Expression of SGLT1, Bcl-2 and p53 in primary pancreatic cancer related to survival. Cancer Invest. 2008; 26:852–9.
7. Normanno N, et al. Epidermal growth factor receptor (EGFR) signaling in cancer. Gene. 2006;366:2–16.
8. Lv Y, Chen W, Zhao P. Clinicopathological correlative analysis of epidermal growth factor receptor gene in colorectal carcinoma. Chin J Cancer Prev Treat. 2008;15:206–10.
9. Wei XY, et al. Expression and significance of EGFR and VEGF in colorectal carcinoma. Chin Clin Oncol. 2009;14:895–9.
10. Spano JP, et al. Impact of EGFR expression on colorectal cancer patient prognosis and survival. Ann Oncol. 2005;16:102–8.
11. Galizia G, et al. Prognostic significance of epidermal growth factor receptor expression in colon cancer patients undergoing curative surgery. Ann Surg Oncol. 2006;13:823–35.
12. Abd El All HS, Mishriky AM, Mohamed FA. Epidermal growth factor receptor in colorectal carcinoma: correlation with clinicopathological prognostic factors. Colorectal Dis. 2008;10:170–8.
13. Khalifa MA, et al. Expression of epidermal growth factor receptor in primary colorectal adenocarcinoma predicts expression in recurrent disease. Am J Clin Pat hol. 2006;125:229–33.

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