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ORIGINAL ARTICLE

Expression and clinical significance of CD90 and CD177 tumor stem cell markers in cervical cancer

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Abstract

Objective To investigate the expression and clinical significance of CD90 and CD177 in cervical cancer.
Methods Cases of cervical cancer (n = 102), cervical intraepithelial neoplasia (CIN, n = 52), and benign uterine disease (n = 50) were selected. The positive rates of CD90 and CD177 in the cervical tissues were detected, and the significance of CD90 and CD177 expression was analyzed.
Results The positive rate of CD90 in normal cervical tissue, CIN, and cervical cancer was 3.7%, 36.5%, and 79.4% respectively. The respective positive rates of CD177 were 1.8%, 32.7%, and 74.5%. The positive rates of CD90 and CD177 in cervical cancer tissues were the highest, followed by CIN tissues (P < 0.05). Multivariate analysis showed that pathological grade, lymph node metastasis, and tumor diameter were independent risk factors affecting the expression of CD90 and CD177 (each P < 0.05). There was a moderate positive correlation between CD90 and CD177 expression (r = 0.679, P = 0.003). The overall survival rate of 102 patients with cervical cancer was 64.7%. There were 33 deaths in the CD90 positive group and 3 in the negative group. The overall survival rates were 59.3% and 85.7% in the CD90 and negative group, respectively. There were 33 deaths in the CD177 positive group and 3 in the negative group. The overall survival rates were 56.6% and 88.5%, respectively. The difference was statistically significant.
Conclusion The expression of CD90 and CD177 has some adverse effects on the clinicopathological parameters of cervical cancer. The positive expression of CD90 and CD177 is a risk factor for poor prognosis.

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Key words: CD90; CD177; cervical cancer

Cervical cancer is one of the most common malignant tumors in women. With the gradual changes in female sexual attitudes and living habits, the incidence of morbidity has become significantly greater in younger women [1]. Tumor stem cells are a group of special tumor cells that can maintain the vitality of tumor cell populations through self-renewal and infinite proliferation, and are currently a research hotspot of tumor-targeted therapy [2–3]. CD90 and CD177 are commonly used markers of cancer stem cells, but no reports exist on the differential expression of CD90 and CD177 in normal cervical tissues, cervical intraepithelial neoplasia (CIN) tissues, and cervical cancer tissues.

Presently, 102 cases of cervical cancer, 52 cases of CIN, and 50 cases of benign uterine disease were studied to investigate the expression of the two in different cervical lesions and the clinical pathological parameters and prognosis of cervical cancer, in order to compare the relationship between cancer stem cells and cervical cancer. The study provides more experimental evidence.

Materials and methods

Research subjects

Patients with cervical cancer and CIN admitted to the Third People's Hospital in Yancheng from January 2015 to December 2017 were enrolled. Inclusion criteria included diagnoses by pathological means, initial diagnosis, surgical treatment, stage I or stage IIa, and the lack of anti-tumor therapy, such as radiotherapy and chemotherapy, before surgery. Exclusion criteria included history of malignant

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tumors and incomplete follow-up information. Finally, 52 patients with CIN and 102 patients with cervical cancer were included in the study. As well, 54 patients with benign diseases, such as uterine fibroids, were treated as normal controls.

Reagents and immunohistochemical staining

Rabbit anti-human CD90, rabbit anti-human CD177 polyclonal antibody, and SP kit were purchased from TaKaRa Bio (Shiga, Japan). Tissue was preserved in the pathology department of our hospital, and involved formaldehyde fixation, paraffin embedding, and routine dewaxing and hydration after sectioning. High temperature repair antigen, phosphate buffered saline (PBS) rinse, blocking antibody. Fifty microliters of rabbit anti-human CD90 polyclonal antibody was added dropwise and incubated overnight. The secondary antibody was added dropwise after PBS washing, and the reaction occurred in the presence of 3,3'-diaminobenzidine (DAB) was developed. Brown particles were used as a positive standard.

Follow-up

The patients were followed-up by clinic visits and telephone contact. The follow-up period began with radical surgery for cervical cancer. The deadline was January 31, 2019. Overall survival (OS) was defined as the time from radical surgery to death from any cause.

Statistical analyses

All data analyses were performed using SPSS 20.0 software (SPSS Inc., Chicago, IL, USA). The measurement data is expressed as frequency and rate, with statistical inference based on the chi-square test. Survival analysis was performed using Kaplan-Meier analysis and the log-rank test was used to compare the effects of CD90 and CD177 expression on OS. The test level of significance was $\alpha = 0.05$.

Results

Expression of CD90 and CD177 in cervical tissues

Both CD90 and CD177 were mainly expressed in the cell membrane of tumor cells, with a small amount of expression in the cytoplasm. The positive rate of CD90

Table 1 Positive rates of CD90 and CD177 in different cervical tissues

Index	Normal cervical (n = 54)	CIN (n = 52)	Cervical cancer (n = 102)	χ^2	P
CD90				85.314	0.000
–	52	33	21		
+	2	19	81		
CD177				79.628	0.000
–	53	35	26		
+	1	17	76		

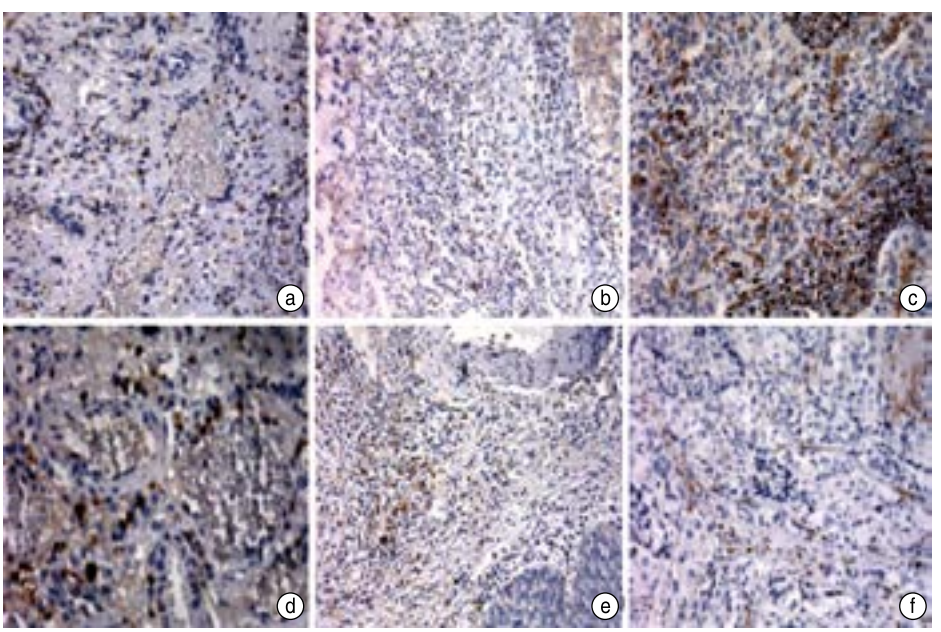

Fig. 1 Expression of CD90 and CD177 in different cervical tissues. (a) CD90 is expressed in normal cervical tissues; (b) CD90 is expressed in CIN tissues; (c) CD90 is expressed in cervical cancer tissues; (d) CD177 is expressed in normal cervical tissues; (e) CD177 is expressed in CIN tissues; (f) CD177 is expressed in cervical cancer tissues

in normal cervical, CIN, and cervical cancer tissues was 3.7% (2/54), 36.5% (19/52), and 79.4% (81/102), respectively. It was 1.8% (1/54), 32.7% (17/52), and 74.5% (76/102), respectively. After pairwise comparison, CD90 and CD177 displayed the highest positive rates in cervical cancer tissues, followed by CIN tissue, with the lowest positive rate in normal tissues. The difference was statistically significant ($P < 0.05$) (Table 1, Fig. 1).

Univariate analysis of the influence of CD90 and CD177 expression on pathological parameters of cervical cancer

Univariate analysis showed that CD90 and CD177 expression had significant effects on pathological grade, lymph node metastasis, and tumor diameter (each $P < 0.05$), but had no significant correlation with age, histological type, FIGO stage (each $P > 0.05$) (Table 2).

Multivariate analysis of the influence of expression of CD90 and CD177 on cervical cancer

All the significant indicators in the univariate analysis were included in the logistic risk model. Pathological grade, lymph node metastasis, and tumor diameter were independent risk factors for the expression of CD90 and CD177 (each $P<0.05$) (Table 3 and Table 4).

Correlation analysis of CD90 and CD177 expression in cervical cancer tissues

Spearman rank correlation test showed a positive correlation between CD90 and CD177 expression (r=0.679, P=0.003) (Table 5).

Table 2 Univariate analysis of the effects of CD90 and CD177 expression on pathological parameters of cervical cancer

index	CD90		χ^2	P	CD177		χ^2	P
	–	+			–	+		
Age (years)			0.031	0.861			0.106	0.745
≤ 45	9	33			10	32		
> 45	12	48			16	44		
Histological Type			0.038	0.845			0.039	0.843
Adenocarcinoma	4	17			5	16		
Squamous cell carcinoma	17	64			21	60		
FIGO stage			1.757	0.185			3.740	0.053
I	13	37			17	33		
II	8	44			9	43		
Pathological classification			22.985	0.000			7.607	0.022
Well-differentiated	9	4			7	6		
Moderately differentiated	9	41			13	37		
Poorly differentiated	3	36			6	33		
Lymphatic metastasis			9.520	0.002			9.177	0.002
Yes	0	27			1	26		
No	21	54			25	50		
Tumor diameter (cm)			7.708	0.005			4.444	0.035
< 3	14	27			15	26		
≥ 3	7	54			11	50		

Table 3 Effect of CD90 expression on pathological parameters of cervical cancer

Index	β	SE	Wald	95%CI	OR	P
Pathological classification	1.372	0.417	10.823	1.741–8.929	3.943	< 0.001
lymphatic metastasis	1.322	0.408	10.455	1.686–8.345	3.767	< 0.001
Tumor diameter	0.897	0.451	12.298	1.013–5.936	2.492	< 0.001

Table 4 Effect of CD177 expression on pathological parameters of cervical cancer

Index	β	SE	Wald	95%CI	OR	P
Pathological classification	1.398	0.208	18.342	2.692–6.084	4.211	< 0.001
Lymphatic metastasis	1.213	0.429	17.216	1.415–7.798	2.869	< 0.001
Tumor diameter	1.581	0.378	17.356	2.317–10.195	4.829	< 0.001

Table 5 Correlation analysis of CD90 and CD177 expression in cervical cancer tissues

CD90	CD177		*r*	*P*
	–	+		
–	6	15		
+	20	61	0.679	0.003
Total	26	76		

Effects of CD90, CD177 expression on the prognosis of patients with cervical cancer

The follow-up deadline was January 2019. Of the 102 patients with cervical cancer, 36 died and 66 survived, representing a survival rate of 64.7%. There were 33 deaths in the CD90 positive group and 3 deaths in the negative group. The OS rate for the CD90 positive and negative group was 59.3% and 85.7%, respectively. The difference was statistically significant (χ^2 = 4.606, P = 0.031). There were 33 deaths in the CD177 positive group and 3 deaths in the negative group. The respective OS rates were 56.6% and 88.5%. The difference was statistically significant (χ^2 = 5.166, P = 0.023). The results are showed in Fig. 2.

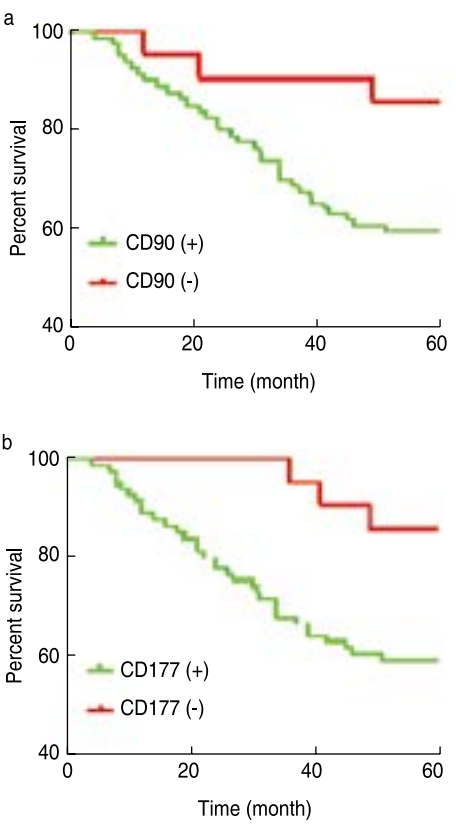

Fig. 2 Survival curves of patients with different CD90 and CD177 expression. (a) CD90 (+), CD90 (–) patient survival curve; (b) CD177 (+), CD177 (–) patient survival curve

Discussion

Cervical cancer refers to the malignant tumor that occurs at the junction with the squamous epithelial cells of the cervix, or transition zone and the columnar epithelial cells of the endocervix of the cervix. The death rate from cervical cancer is the fourth highest overall in China, and is the second leading cause of death in females [4]. Surgery is the preferred method of treatment for cervical cancer, especially in patients with early stage I or IIa [5]. Most (80%) of early cancer patients can achieve good survival through surgical treatment, but a small number of patients will relapse or metastasize in a short period of time even after standard radical surgery [6]. At the same time, for most patients with malignant tumors, radiotherapy and chemotherapy and biological immunotherapy can kill most tumor cells, but these approaches cannot fundamentally cure the tumor. This may be related to the presence of tumor cells with stem cell properties in the circulating blood [7].

Tumor stem cells have the characteristics of self-renewal, heterogeneity, and infinite proliferation, which can efficiently produce tumor cells. Surface molecules, such as CD44 and CD199, are commonly used molecules for screening cancer stem cells [8]. In cervical cancer, current research focuses on CD133, Bmi-1, p63, Oet3/4, and other molecules [9]. CD44 and CD199 are widely distributed; they are multi-molecular forms of membrane integrin, including extracellular, transmembrane, and cytoplasmic regions, which are mainly involved in mediating the interaction between cells and cells (between extracellular matrices) [10]. The main functions of the two include [11] mediating cell-to-cell adhesion by interacting with fibronectin and collagen, auxiliary or direct involvement in the uptake and degradation of hyaluronic acid, participation in lymphocyte homing, and promotion of T cell activation.

These aspects have been extensively studied in studies of gastric cancer, colon cancer, and prostate cancer, but little research has been done in cervical cancer. In this study, we found that CD90 and CD177 had the highest positive rate in cervical cancer tissues, followed by CIN tissue, with the lowest positive rate in normal tissues. The difference was statistically significant. This is consistent with the expression of malignant markers in progressive lesions. Multivariate logistic analysis showed that pathological grade, lymph node metastasis, and tumor diameter were independent risk factors for the expression of CD90 and CD177. As the pathological grade worsened, tumor malignancy increased and cell proliferation accelerated. As the expression of CD90 and CD177 increased, the degree of differentiation of cervical cancer was progressively reduced, consistent with previous findings [12]. The diameter of the tumor can directly reflect

the tumor burden of the whole body of the patient. The higher the expression of CD90 and CD177, the higher the tumor burden of the patient. Based on the study of the influence of the expression on tumor diameter and differentiation, we followed the patients and found that the OS rate of the 102 patients with cervical cancer was 64.7%. The OS rate of the CD90-positive group was 59.3%, and that of the CD177-positive group was 56.6%. The difference was statistically significant compared with the corresponding negative group, indicating that the positive expression of both has a significant adverse effect on the survival of patients.

In summary, the expression of CD90 and CD177 has a certain adverse effect on the clinicopathological parameters of cervical cancer, and the positive expression of both is a risk factor for poor prognosis. However, this study is a single-center study that used a less sensitive immunohistochemistry method. Multi-center combination, increased sample size, and improved detection technology are needed to provide conclusive clinical evidence.

Conflicts of interest

The authors declare that they have no competing interests.

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