Original Article

Expression of CYB5D2 is associated with epithelial-mesenchymal transition and survival rates in patients with cervical cancer

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Background: CYB5D2 is a member of the membrane-associated progesterone receptors (MAPRs) family and plays essential roles in regulating nerve development. CYB5D2 is associated with tumor suppression in breast cancer. Despite the potential implication of CYB5D2 in cancer progression, its level and clinical significance in cervical cancer tissues has not been investigated yet. Via this study, we aimed to investigate the possible role played by CYB5D2 in epithelial–mesenchymal transition (EMT) in cervical cancer and correlate its level with clinical outcomes.

Methods: The expressions of CYB5D2 and the EMT marker E-cadherin in different groups of cervical samples were compared using immunofluorescence. Furthermore, co-localization of CYB5D2 and E-cadherin was analyzed in different cervical tissue samples via confocal laser scanning microscopy. The relationship between CYB5D2/E-cadherin and the progression and clinicopathological features of cervical cancer were analyzed, and the prognostic value of CYB5D2 mRNA expression was evaluated in various tumors using the Kaplan-Meier plotter database.

Results: CYB5D2 and E-cadherin were downregulated in cervical cancer ($P<0.05$). Co-localization of CYB5D2 and E-cadherin in cell cytoplasm in cervical cancer was apparent. The clinical and pathological information of patients with cervical cancer were analyzed, which revealed a statistically significant relationship between low CYB5D2 expression and the tumor FIGO stage ($P<0.05$). CYB5D2 expression was not correlated with tumors in terms of depth of myometrial invasion, patient age, histological type, and tumor grade ($P>0.05$). Higher expression levels of CYB5D2 mRNA were predicted to be associated with a better relapse-free survival (RFS) in patients with cervical cancer. E-cadherin expression was associated with invasive tumors, tumor grade, and FIGO stage ($P<0.05$) but not with patient age and histological type ($P>0.05$). There was a positive correlation between CYB5D2 and E-cadherin expression in cervical cancer ($P<0.01$).

Conclusions: These results suggest that CYB5D2 acts as a tumor suppressor in cervical cancer, inhibiting EMT by hindering E-cadherin expression.

Keywords: CYB5D2; E-cadherin; cervical cancer; epithelial–mesenchymal transition

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Introduction

Cervical cancer (CC) is one of the most common gynecological malignancies observed in clinics, and it poses a serious threat to women's health and lives. According to the latest report on the prevalence of malignant tumors, there were approximately 569,847 new cases of CC worldwide in 2018. Of these, 311,365 patients died. In China, the incidence rate is 6.24%, and the overall mortality rate is 3.96% (1). Cervical tumors are more common in economically less-developed areas of society, and the age at disease onset in these areas tends to be less (2). Considering the popularity of cervical cytology screening and the advent of CC vaccines, most CC lesion can be diagnosed early and has a good prognosis. Currently, clinical treatment of CC is based on surgery and radiotherapy, supplemented by chemotherapy; however, the prognosis is relatively poor in patients with advanced or recurrent metastasis. Therefore, the main focus in the field of CC research has been the development of tumors and search for new therapeutic targets.

CYB5D2 is located on chromosome 17p13.2. The product encoded by the gene is a secreted protein comprising 64 amino acids, and it belongs to the family of membrane-associated progesterone receptors (MAPRs) (3). In recent years, MAPR family proteins have been found to be expressed abnormally in a range of malignant tumors and to participate in the regulation of tumorigenesis, tumor proliferation, metastasis, and chemotherapeutic drug sensitivity. They are expected to become new molecular diagnostic markers and therapeutic targets for tumors (2). Additionally, CYB5D2 has been found to significantly inhibit lung metastasis in immunodeficient mice and HeLa cell invasion in vitro and promote the survival of HeLa cells exposed to chemotherapeutic agents such as paclitaxel, cisplatin, and doxorubicin (4).

The epithelial–mesenchymal transition (EMT) is a main way in which tumor cells acquire invasive and migratory properties (5,6). EMT refers to the process by which biological epithelial cells are transformed into mesenchymal cells, and the decrease in E-cadherin expression is a landmark event in which EMT occurs (7,8). E-cadherin is an adhesion molecule in epithelial cells and significantly contributes toward maintaining the integrity of normal epithelial cells. In recent years, it has been found that E-cadherin is expressed stably in normal cells and that its expression is either downregulated or suppressed in various epithelial tumors, which reduces the adhesion between cells (9-12). When the conditions of metastasis are mature, the cancer cells can be invaded and metastasized from the primary tumor (13-15). In estrogen receptor-positive breast cancer, E-cadherin enhances cancer cell invasion and metastasis (16-18). Conversely, E-cadherin can be used as an independent predictor of early CC prognosis. As per survival analyses conducted using the Kaplan–Meier plotter database, high transcription levels of CYB5D2 were associated with improved RFS in patients with CC. CYB5D2 also increased HeLa cell migration and invasion *in vitro*. Thus, we hypothesized that CYB5D2 inhibits EMT in CC.

We examined the expression of CYB5D2 and E-cadherin in different types of cervical tissues and analyzed the correlation between their expression and clinicopathological parameters to ascertain their potential function and prognostic value in CC.

Methods

Patients and samples

In total, 141 cervical microarray tissue samples were purchased from Xi'an Elena Biotech (CR208, CR1001a, and BB10011, Xi'an Elena Biotech, China). Samples for which all clinical data and adequate tumor specimens were available were included. Clinical information for each sample included interstitial infiltration depth, lymph vessel spatial invasion, regional lymph node metastasis, histological tumor grade, and FIGO stage. Pathological diagnosis of each sample was based on the corresponding hematoxylin–eosin (HE) staining combined with the American Joint Committee on Cancer (AJCC, 2017) staging system.

Immunofluorescence (IF)

The cervical microarray tissue samples used for the experiment were placed in an oven at 65 ℃ for 30 min. They were permeabilized in TO bio-clearing agent for 15 min and washed in 100% alcohol, 95% alcohol, and 70% alcohol for 5 min each time. Once the tissue chip was washed, it was placed in a pre-warmed sodium citrate antigen repair solution, heated in a medical microwave oven for 10 min, equilibrated to room temperature, and blocked for 1 h in a phosphate buffer containing 3% bovine serum albumin. Subsequently, it was incubated overnight at 4 ℃ with primary antibodies against E-cadherin (mouse monoclonal, 1:100, Invitrogen, USA) and CYB5D2 (rabbit

polyclonal, 1:50, Santa Cruz Biotechnology, USA). Next, it was washed three times with PBS for 15 min each time. The tissue microarray was incubated with FITC-conjugated AffiniPure donkey anti-rabbit IgG (1:200, Jackson Immuno Research, USA) and Cy3-conjugated AffiniPure goat anti-mouse IgG (1:200, Jackson Immuno Research, USA) for 1 h at 37 ℃. Finally, the nucleus was stained with 4',6-diamidino-2-phenylindole dihydrochloride (DAPI), and fluorescence imaging was performed using a laser confocal microscope (Nikon AIR +, Japan).

Kaplan–Meier plotter

The prognostic value of CYB5D2 mRNA expression was assessed using an online database, the Kaplan–Meier Plotter (www.kmplot.com), which contains gene expression data and survival information on 304 patients with cervical squamous cell carcinoma. To analyze relapse-free survival (RFS) of patients with CC, patient samples were divided into two groups based on median expression (high *vs.* low expression) and assessed using a Kaplan–Meier survival plot by a hazard ratio with 95% confidence intervals and log-rank P value.

Statistical analysis

The experimental data were statistically analyzed using IBM SPSS 22.0 for Windows (SPSS Inc., Chicago, IL, USA) and GraphPad Prism 6.0 software (GraphPad Software, Inc., USA). A Mann–Whitney U test was used to test the two groups based on different clinical features. Data analysis and statistical comparison between multiple groups were performed by one-way analysis of variance followed by a SNK-q test. The Spearman rank correlation coefficient was calculated to analyze the correlation between CYB5D2 and E-cadherin expressions, and a linear regression was then performed. Differences were considered significant at $P<0.05$.

Results

Clinicopathological features

The median age of the 141 patients in the study was 44 years (range, 15–75 years). In total, 19 patients (13.5%) had normal cervical tissue, 23 (16.3%) had cervical intraepithelial neoplasia (CIN), and 99 had CC tissue (70.2%). Of these 99 patients, 64 (64.6%) had cervical squamous cell carcinoma, 30 (30.3%) had adenocarcinoma, and 5 (5.1%) had adenosquamous carcinoma. Cancer infiltration in 20 (22.5%) patients was deeper than the uterus; 10 (10.1%) patients had lymph node metastasis. In total, 17 (18.1%) patients had well differentiated (G1), 51 (54.3%) had moderately differentiated (G2), and 26 (27.7%) had poorly differentiated (G3) tumors. The clinical FIGO stages of the CC research cases include stages I, IA, IA1, IA2, IB, IB1, IB2, II, IIA, IIB, III, IIIB, and IVA. In addition, 110 (78.0%) patients with HPV infection had high-risk cervical precancerous lesions and tumor tissues, and 31 (22.0%) patients without HPV infection had normal cervical tissues and some low-risk cervical precancerous lesions. The specific clinical pathology data are summarized in *Table 1*.

As CC progresses, both CYB5D2 and E-cadherin are downregulated

To investigate the role played by CYB5D2 in CC carcinogenesis and its relationship with the EMT-related marker protein E-cadherin, we examined the expression of CYB5D2 and E-cadherin in normal cervical tissues, CIN, and tumors. The findings revealed that CYB5D2 expression (*Figure 1*) decreased gradually following CC development, and there were significant changes in its expression in normal and CC tissues, with the difference being statistically significant ($P<0.05$, *Figure 2A*). Additionally, the expression of E-cadherin (*Figure 1*) decreased gradually as cervical carcinogenesis progressed, and the difference between the two groups was statistically significant ($P<0.05$, *Figure 2B*). The findings of this study indicate that the downregulation of CYB5D2 and E-cadherin is statistically significant in normal cervical tissue or cervical precancerous tissue compared with that in CC tissue. Furthermore, CYB5D2 and E-cadherin appear to be co-localized in the cell cytoplasm in all cervical tissue.

Increased expression level of CYB5D2 mRNA is associated with better RFS in patients with various tumor types

The Kaplan-Meier curve and log-rank test analyses revealed a significant association between the CYB5D2 mRNA expression levels and RFS ($P<0.05$) (*Figure 3*) in patients with various tumor types. Patients with higher mRNA levels of CYB5D2 factors were predicted to have better RFS. Therefore, CYB5D2 acts as a tumor suppressor and affects the prognosis and survival of patients with various tumors;

Table 1 Clinicopathologic characteristics of all patients

Clinicopathologic characteristics	No. of patients (%)
Age	
<44 years	66 (46.8)
≥44 years	75 (53.2)
Type of patients	
Normal	19 (13.5)
CIN (I–III)	23 (16.3)
Tumor	99 (70.2)
Histologic grade	
G1	17 (18.1)
G2	51 (54.3)
G3	26 (27.7)
Myometrial invasion	
<T2	69 (77.5)
≥T2	20 (22.5)
Distant metastasis	
Negative	89 (89.9)
Positive	10 (10.1)
Histological type	
Squamous cell carcinoma	64 (64.6)
Adenocarcinoma	30 (30.3)
Adenosquamous carcinoma	5 (5.1)
FIGO stage	
I	16 (18.0)
IA	6 (6.7)
IA1	5 (5.6)
IA2	1 (1.1)
IB	22 (24.7)
IB1	7 (7.9)
IB2	6 (6.7)
II	5 (5.6)
IIA	2 (2.2)
IIB	7 (7.9)
III	2 (2.2)
IIIB	9 (10.1)
IVA	1 (1.1)
HPV infection	
Yes	110 (78.0)
No	31 (22.0)

FIGO indicates American Joint Committee on Cancer (AJCC, 2017) staging.

thus, it can be used as potential target for precision therapy in patients with cancer. These data also show that CYB5D2 is a new biomarker for CC prognosis.

Correlation of CYB5D2/E-cadherin with clinicopathological features

As shown in *Table 2*, the correlation of EMT-associated markers and CYB5D2 with clinicopathological features was analyzed. Analysis of the clinical and pathological information of patients with CC revealed a statistically significant relationship between CYB5D2 expression and FIGO stage. Specifically, compared with the FIGO stage (I + II), CYB5D2 expression was observed to be lower in stage III tumors (P=0.008). Similarly, E-cadherin expression was decreased in the FIGO stage III compared with stage (I + II) (P=0.012). CYB5D2 expression showed no difference between tumors with respect to myometrial invasion (P=0.550), patient age (P=0.682), histological type (P=0.078), and tumor grade (P=0.581). Remarkably, E-cadherin expression was significantly lower in poorly differentiated tumors (G3) than that in well-differentiated and moderately differentiated tumors (G1 + G2) (P<0.001). We also found that E-cadherin expression decreased in cases of deeply invasive tumors compared with that in cases of superficial myometrial invasion (P=0.040). Finally, there was no relationship between E-cadherin expression in patients with CC and patient age (P=0.246) and its histological type (P=0.057).

CYB5D2 expression is positively correlated with E-cadherin expression in patients with CC

Our previous findings indicated that CYB5D2 and E-cadherin expressions are downregulated in CC tissues. Furthermore, to assess the expression of CYB5D2 and E-cadherin in different groups, we performed a Spearman rank correlation analysis, and the results showed that CYB5D2 and E-cadherin were positively correlated between different groups, and this was statistically significant (*Figure 4*). CYB5D2 and E-cadherin expressions were downregulated in patients with CC.

Discussion

CYB5D2 is a member of the progesterone membrane receptor-associated family and relies on the binding of heme to its cytochrome b5-like heme/steroid domain to

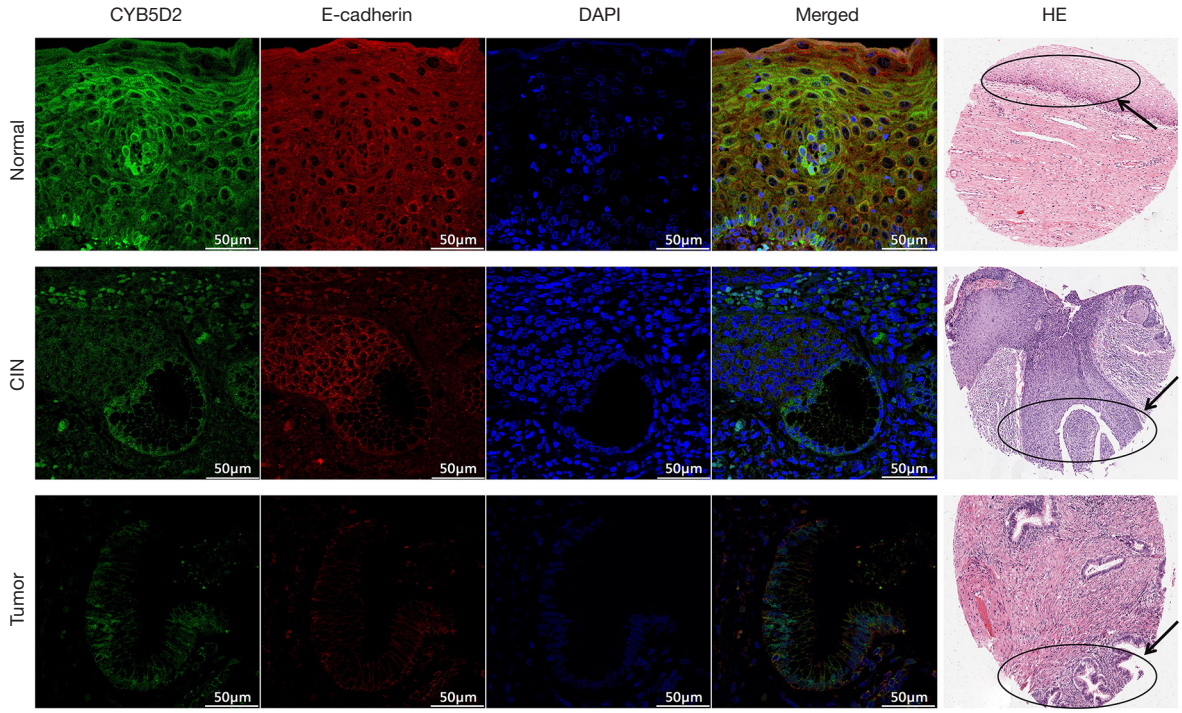

Figure 1 Immunofluorescence staining showing CYB5D2 expression (green) and location (red) of E-cadherin in various cervical tissues (Magnification: ×600, scale =50 μm). The nucleus is stained with DAPI (blue).

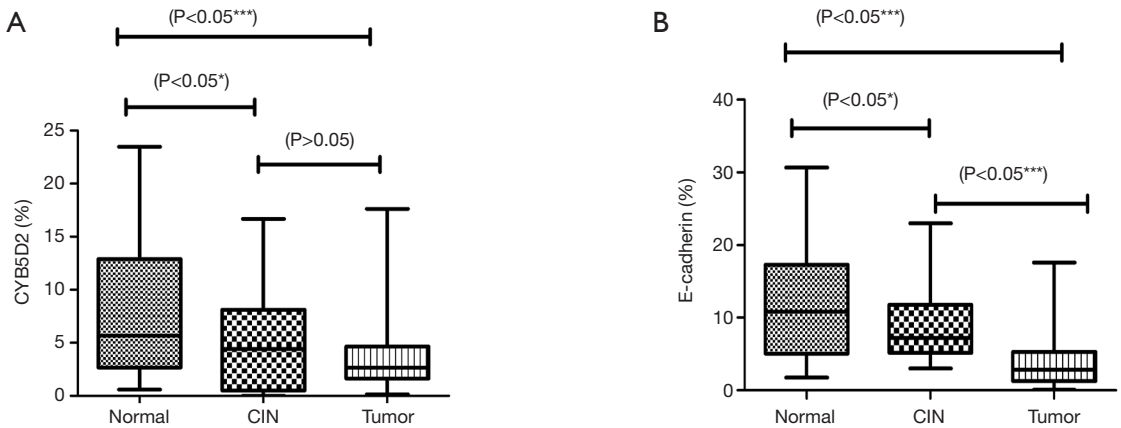

Figure 2 Expressions of CYB5D2 and E-cadherin proteins in different tissue groups and comparison between groups. (A) Expression of CYB5D2 proteins in normal cervical tissues (n=19), CIN (n=23), and tumor tissues (n=99). (B) Expression of E-cadherin proteins in normal cervical tissues (n=19), CIN (n=23), and tumor tissues (n=99).

exert biological activity (19). It is well known that CYB5D2 expression is downregulated in diverse cancers and act as tumor suppressors (8,20). In the latest research, it has been reported that CYB5D2 is associated with tumor suppression function in breast cancer. CYB5D2 expression was significantly decreased in tamoxifen-resistant MCF7 cells and in MCF7 cell-derived xenografts treated with TAM. CYB5D2 overexpression induced apoptosis in MCF7 cells, and CYB5D2 knockdown enhanced MCF7 cell proliferation. Downregulation of CYB5D2 expression decreased overall survival of patients with breast cancer, which indicates that *CYB5D2* plays a role as a tumor

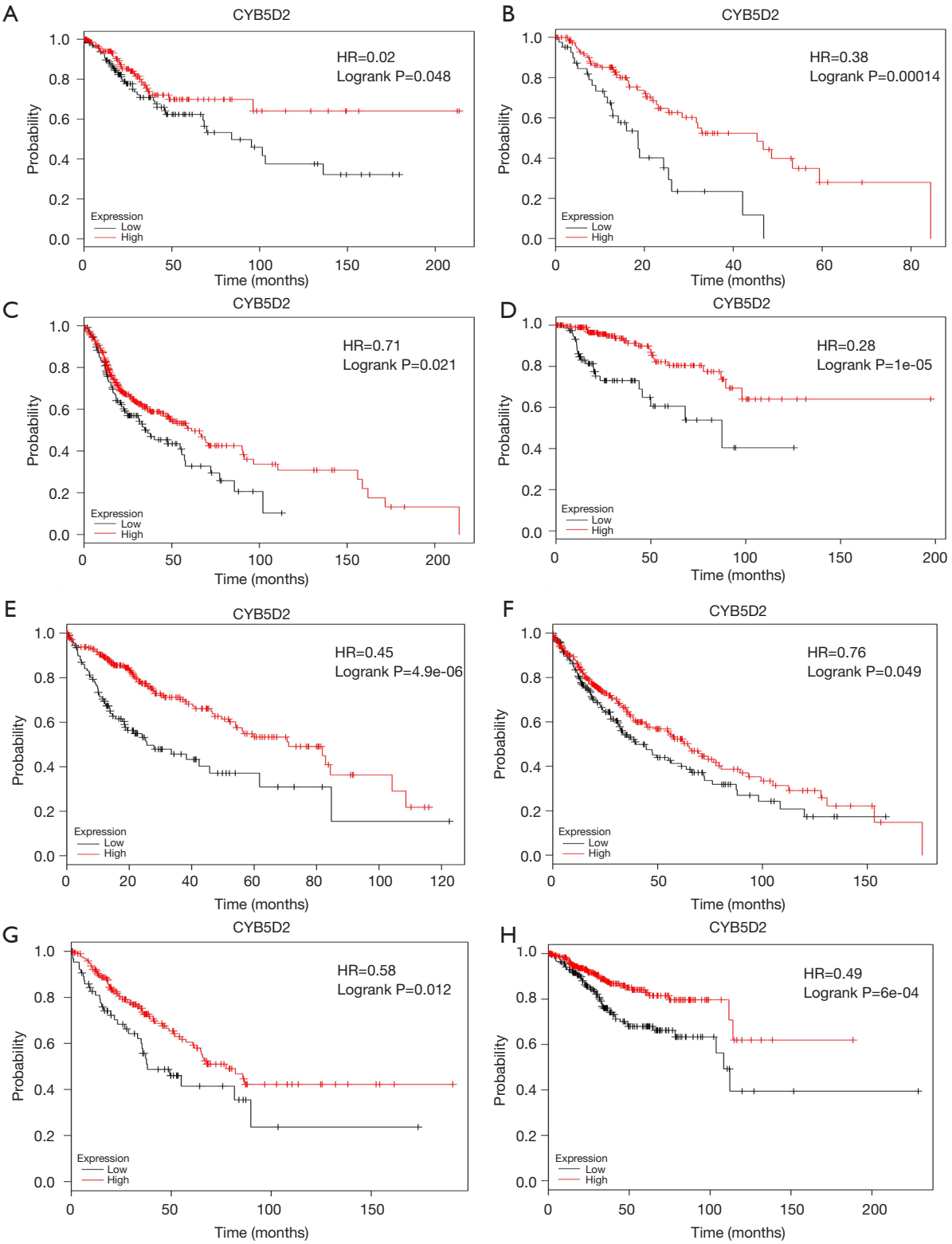

Figure 3 Prognostic value of the mRNA expression level of CYB5D2 in patients with various tumor types (RFS in the Kaplan–Meier plotter). (A) Cervical squamous cell carcinoma, (B) esophageal carcinoma, (C) head-neck squamous carcinoma, (D) kidney renal papillary cell carcinoma, (E) liver hepatocellular carcinoma, (F) lung squamous cell carcinoma, (G) sarcoma, (H) uterine corpus endometrial carcinoma.

Table 2 Correlation of EMT-associated markers and CYB5D2 with clinicopathologic features in CC

Clinicopathologic features	CYB5D2		E-cadherin	
	No. of patients	P	No. of patients	P
Age, years		0.682		0.246
<47	48		48	
≥47	51		51	
Histological grade		0.581		<0.001*
G1+G2	69		69	
G3	25		25	
Myometrial invasion		0.550		0.040*
<T2	69		69	
≥T2	20		20	
FIGO stage		0.008*		0.012*
I–II	77		77	
III	12		12	
Histological type		0.078		0.057
Squamous carcinoma	64		64	
Adenocarcinoma	30		30	
Lymph node metastasis		0.224		0.386
Negative	89		89	
Positive	10		10	

*, statistically significant. T2: the infiltration range is beyond the uterus.

suppressor in patients with CC. In the present study, we analyzed CYB5D2 expression in various cervical tissues and found that CYB5D2 expression was downregulated in CC tissues compared with that in normal cervical or CIN tissue, suggesting a relationship between CYB5D2 and the pathogenesis of cervical cancer (21).

EMT is an important pathological link leading to the progression of cervical lesions. This process specifically refers to the transformation of epithelial cells from an epithelial phenotype to an interstitial phenotype under the influence of a specific environment and inducement, characterized by decreased expression of the epithelial cell markers E-cadherin and β-catenin and increased expression of the interstitial cell phenotypes N-cadherin and vimentin (13). During EMT, cells lose their polarity, and their connection with the basement membrane loosens; this promotes strong migration and invasion by tumor cells. Cadherin, a transmembrane glycoprotein involved in cell–cell attachment, is categorized into the following three types: E-cadherin, P-cadherin, and N-cadherin. E-cadherin maintains tight junctions between cells and blocks tumor cell invasion and metastasis. Re-expression of E-cadherin by invasive tumor cells can reverse the invasiveness of tumor cells. Currently, downregulation of E-cadherin expression is considered to be the most prominent feature of EMT. E-cadherin belongs to the cadherin protein family and is mainly expressed in the epithelial cell membrane. It is critical for the formation and maintenance of adherent junctions in areas of epithelial cell–cell contact. E-cadherin is an important tumor suppressor, and downregulation of E-cadherin expression can promote EMT, a critical process for the metastasis and invasion by malignant tumors originating in the epithelial. As an important EMT regulator, loss of E-cadherin suppresses cell adhesion and polarity, which promotes EMT in tumor cells (22). It has been suggested that E-cadherin serves is an important

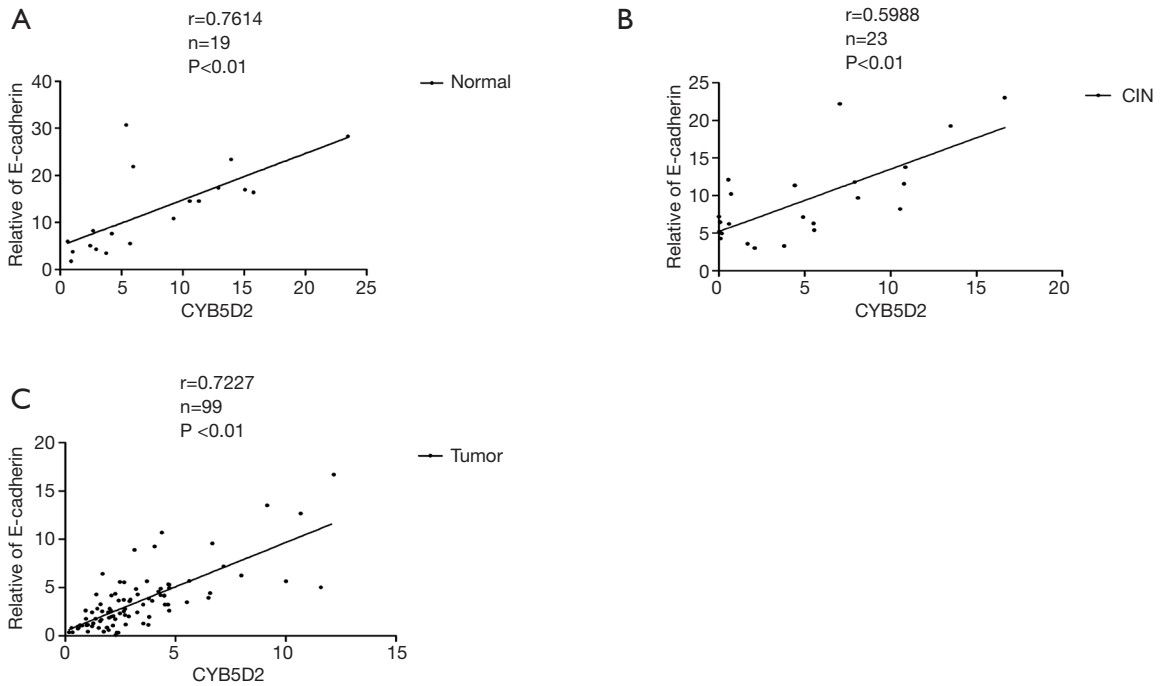

Figure 4 Spearman rank correlation analysis revealed CYB5D2 expression to be correlated positively with E-cadherin expression in different types of cervical tissues. (A) In normal cervical tissues, CYB5D2 is correlated positively with E-cadherin expression (n=19, r=0.7614, P<0.01). (B) In CIN tissues, CYB5D2 is correlated positively with E-cadherin expression (n=23, r=0.5988, P<0.01). (C) In the CC group, CYB5D2 expression is also correlated positively with E-cadherin expression (n=99, r=0.7227, P<0.01).

biomarker of tumor malignancy, metastasis, recurrence, and prognosis of CC (23). In the present study, E-cadherin was found in the cell membrane of all the cervical tissues examined, indicating that E-cadherin may be related to cell adhesion mediation. Our results show that the expression of E-cadherin in CC is significantly downregulated compared with that in CIN and normal cervical tissues, suggesting the involvement of E-cadherin in EMT in patients with CC. Moreover, results of multiple studies have indicated that increased E-cadherin expression is associated with better overall survival in patients with tumor (24), particularly in the group of patients with lymph node metastasis (25,26), which may be an indicator of CC prognosis. A limitation of our study is the small number of samples and that no data are available on the evolution of patients with CC to evaluate the relationship of CYB5D2 and E-cadherin expressions with invasive tumor capacity and survival of patients. However, we performed a statistical analysis of the relevant clinical pathology based on the available data. First, we studied the relationship between CYB5D2 expression and clinicopathological features of CC. A lower clinical stage corresponded with lower expression levels of CYB5D2, suggesting that CYB5D2 plays a certain inhibitory role in CC evolution. Although CYB5D2 expression does not significantly differ based on the patient's age, histological type, and grade, the statistical significance of its expression may be limited by a small sample size, and further studies evaluating larger samples are required. We also used bioinformatics to explore the correlation between CYB5D2 and RFS with different tumors; for instance, we analyzed the RFS of 304 patients with cervical squamous cell carcinoma and found that a high expression level of CYB5D2 mRNA was associated with a longer RFS. Similar results were found for patients with other cancers, further suggesting that CYB5D2 plays a role in suppressing cancer with cervical lesions and is an evaluation index for assessing the prognosis of CC. Moreover, the results were obtained when the expression pattern of EMT-related proteins was compared with the depth of myometrial invasion, tumor grade, and FIGO stage. Lower the grade, poorer the differentiation, and deeper the infiltration depth, lower the expression of E-cadherin. However, these results were not associated with patient age and histological classification. The study suggests that an abnormal expression of E-cadherin in CC

tissues is highly correlated with the pathological features of invasion and migration of cervical malignant tumors, and it can be used for the prognosis and evaluation of CC. Results of multiple studies have indicated that downregulation of E-cadherin expression promoted lymph node metastasis (27,28). Although results of some studies have indicated that downregulation of E-cadherin expression is associated with lymph node metastasis, there is no correlation between them, as assessed in this study. Further, only 10 patients with lymph node metastasis were included in the study, which may not be representative of the general population. However, we analyzed the correlation between CYB5D2 and E-cadherin expressions in normal tissues, CIN, and tumor tissues and found a clear positive correlation between CYB5D2 and E-cadherin, indicating that CYB5D2 may function as a tumor suppressor in CC by inhibiting E-cadherin expression via EMT.

Conclusions

In summary, based on our findings of cervical tissue microarray samples, it was indicated that downregulation of CYB5D2 expression in CC development is accompanied by the suppression of E-cadherin expression. Meanwhile, CYB5D2 affects the prognosis and survival of patients with CC. The effects of CYB5D2 on the biological function of levels, molecular mechanisms, and in animal models will be used to analyze specific signaling pathways involved in the inhibition of EMT to further clarify the mechanism by which CYB5D2 acts as a tumor suppressor in patients with CC. We will furnish promising strategies for the treatment of CC.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2020.01.03). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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