Int J Clin Exp Med 2024;17(11):198-205
www.ijcem.com /ISSN:1940-5901/IJCEM0159298

Original Article

Overexpression of DOCK6 correlates with poor survival of patients with epithelial ovarian cancer

Ping Wang[1,2], Hong Liao[2,3], Juan Zou[2,4], Quyou Wang[5], Shujun Bai[2], He Wang[1,2], Shanling Liu[1,2]

[1]Department of Medical Genetics/Prenatal Diagnostic Center, West China Second University Hospital, Sichuan University, Chengdu, Sichuan, China; [2]Key Laboratory of Birth Defects and Related Diseases of Women and Children (Sichuan University), Ministry of Education, Chengdu, Sichuan, China; [3]Department of Obstetrics and Gynecology, West China Second University Hospital, Sichuan University, Chengdu, Sichuan, China; [4]Department of Pathology, West China Second University Hospital, Sichuan University, Chengdu, Sichuan, China; [5]Prenatal Diagnosis Center, Affiliated Hospital of Guizhou Medical University, Guiyang, Guizhou, China

Received July 18, 2024; Accepted October 25, 2024; Epub November 15, 2024; Published November 30, 2024

Abstract: Objective: To investigate the role of the dedicator of cytokinesis 6 gene (DOCK6) in epithelial ovarian cancer (EOC). Methods: The expression of DOCK6 was measured through immunohistochemistry in samples from sixty-five EOC patients. The correlations between DOCK6 immunoreactivity and different clinicopathological characteristics were determined by Pearson's χ^2 test or Fisher's exact test. Different clinicopathological characteristics in relation to patient survival were evaluated by the Kaplan-Meier survival analysis and multivariate Cox regressions. Results: High DOCK6 expression in EOC tissues was positively associated with an advanced (III+IV) Federation International of Gynecology and Obstetrics (FIGO) stage (P=0.01) and high tumor grade (P=0.01). Using multivariate Cox regressions, DOCK6 expression (P=0.04, HR=2.29, 95% CI=1.06-4.96), FIGO stage (P=0.02, HR=12.15, 95% CI=1.39-106.28) and any residual tumor (P=0.02, HR=3.14, 95% CI=1.19-8.27) were shown to be independent prognostic factors. Conclusion: The overexpression of DOCK6 in EOC tissues was associated with advanced FIGO stage, suggesting that DOCK6 might be involved in the progression of EOC. More importantly, these data validate DOCK6 expression in addition to two pathological parameters (FIGO stage and residual tumor) as independent prognostic markers for EOC patients.

Keywords: Epithelial ovarian cancer, dedicator of cytokinesis 6 gene, immunohistochemical staining, Kaplan-Meier survival analysis, multivariate Cox regressions

Introduction

Ovarian cancer (OC) is the most lethal malignant gynecological tumor due to having a 5-year survival rate of only 30%, thus it poses a serious threat to women's health. OC can develop from epithelial cells, stromal cells, germ cells, or even from the fallopian tube; however, 90% of OCs are epithelial ovarian cancer (EOC) [1, 2]. OC has the highest mortality rate in gynecological cancers partly because 70% of OC patients are diagnosed at an advanced clinical stage [3]. Although more than 75% of OC patients respond to first-line chemotherapy, women who present with recurrence and chemoresistance have a poor prognosis [4, 5]. Therefore, novel and effective target therapies are urgently needed to further improve the prognosis of advanced stage or recurrent OC patients.

Dedicator of cytokinesis (DOCK) is a protein family of atypical Rho guanine nucleotide exchange factors (GEFs) [6, 7]. Based on structural differences, DOCK 1 through DOCK 11 were divided into four classes (DOCK A-D) [8]. DOCK-A and DOCK-B classes are typical GEFs for Rac family small GTPase 1 (RAC1) specifically, while the DOCK-D subfamily serves as GEFs for cell division cycle 42 (CDC42) [9]. DOCK6 is a member of the DOCK-C class and regulates both RAC1 and CDC42 Rho GTPase activity by exchanging guanosine diphosphate (GDP) to guanosine triphosphate (GTP) [10]. In humans, recessive loss-of-function mutations in both alleles of DOCK6 result in Adams-Oliver

https://doi.org/10.62347/OXRU9072

Syndrome (AOS). AOS is usually characterized by an aplasia cutis congenita and transverse terminal limb defects [11-13]. Several members of the DOCK family relate to tumorigenesis, migration and invasion [14-19]. Indeed, DOCK6 was proposed as a novel independent prognostic factor for predicting outcomes in gastric cancer [20].

However, to the best of our knowledge, the potential role of DOCK6 in OC has not yet been reported. The purpose of this study was to detect the expression of DOCK6 in EOC tissues and correlate this with prognostic factors, i.e. age, Federation International of Gynecology and Obstetrics (FIGO) stage, tumor grade, lymph node metastasis, histologic type, primary therapy and residual tumor.

Materials and methods

Patients and specimens

This was a retrospective study including sixty-five patients (19-80 years; median age, 53 years) with EOC. They underwent ovarian surgery at the West China Second University Hospital, Sichuan University (Chengdu, China) between June 2006 and June 2012. Exclusion criteria were patients who received pre-operative chemotherapy, radiotherapy or hormonal treatments. The control group was comprised of females (41-60 years; median age, 50.4 years) with uterine myoma or mesosalpinx cysts. The Ethics Committee of West China Second University Hospital of Sichuan University gave permission for this study. The participant in the study signed a written informed consent.

The cases were categorized into the following groups: 28 cases of serous carcinoma, 16 cases of clear cell carcinoma, 10 cases of endometrioid carcinoma and 11 cases of mucinous carcinoma. EOC stage was classified according to the FIGO guideline [21].

Immunohistochemistry (IHC)

The EOC specimens were fixed in formalin, embedded in paraffin, then sliced into 4 μm sections. The slides were deparaffinized with xylene (99%, v/v), hydrated in a series of graded alcohols (100, 95, 80 and 50%) and soaked in 3% hydrogen peroxide for 15 min. Subsequently, the tumor sections were heated in a microwave oven submerged in ethylenediaminetetraacetic acid (EDTA) buffer for 8 minutes, followed by a 30 min incubation with 5% bovine serum albumin (BSA) (A8020; Solarbio, Beijing, China) at room temperature to reduce non-specific binding. Sections were reacted with an anti-human DOCK6 polyclonal rabbit antibody (25087-1-AP, 1:250, Proteintech, Wuhan, China) at 4°C overnight and then rinsed 3 times (5 min each) with PBS containing 0.1% Tween-20 (PBST). Slides were incubated for 1 h with a secondary horseradish peroxidase-conjugated goat anti-rabbit IgG (A0208; Beyotime, Shanghai, China) at room temperature. The slides were rinsed 3 times (5 min each) with PBST, then incubated with peroxidase-conjugated streptavidin for 30 min. The complete reaction was revealed by 1% (w/v) 3,3'-diaminobenzidine tetrahydrochloride for 10 min. Finally, the slides were counterstained in 0.5% (w/v) hematoxylin for 5 min. Imaging was performed using an upright Leica DM6B microscope at a magnification of ×200 (Leica Microsystems, Wetzlar, Germany).

Scoring of immunoreactivity

To assess the protein expression of DOCK6 in EOC tissues, we adopted a two-grade scoring method, which was based on the staining intensity and the percentage of positive tumor cells. The intensity of DOCK6 staining was defined as follows: 0 (negative staining), 1 (light yellow), 2 (yellow-brown), and 3 (brown). The percentage of DOCK6-positivity was scored as 0 (negative staining), 1 (1-25% positive), 2 (26-50% positive), 3 (51-75% positive) and 4 (76-100% positive). The final immunoreactivity score (IS) was obtained after multiplying the staining intensity by the percentage of positive cells. For statistical analysis, low expression was defined as IS<5, while high expression was defined as IS≥5 [22, 23].

Statistical analysis

The correlation between the expression of DOCK6 protein and clinicopathological characteristics was performed using Pearson's χ^2 test or Fisher's exact test. To analyze the prognostic value of clinicopathological characteristics in EOC, Kaplan-Meier analysis (univariate analysis) was performed. The survival curve in the two groups were compared using the log-rank

Table 1. Relationship between the expression of DOCK6 and clinicopathological characteristics in EOC

Characteristics	N (%)	DOCK6-positive tumor cells		*P*-value
		Low, n	High, n	
		34	31	
Age (years)				0.93
≤55	36 (55.38)	19	17	
>55	29 (44.62)	15	14	
FIGO stage				0.01
I+II	25 (38.46)	18	7	
III+IV	40 (61.54)	16	24	
Tumor grade				0.01
Low-moderate (G1+G2)	23 (35.38)	17	6	
High (G3)	42 (64.62)	17	25	
Lymph node metastasis				0.07
Negative	35 (53.85)	22	13	
Positive	30 (46.15)	12	18	
Histologic type				0.07
Serous adenocarcinoma	28 (43.08)	11	17	
Non-serous adenocarcinoma	37 (56.92)	23	14	
Primary therapy				0.62
Surgery	4 (6.15)	3	1	
Surgery + others	61 (93.85)	31	30	
Residual tumor				0.19
<1 cm	45 (69.23)	26	19	
≥1 cm	20 (30.77)	8	12	

DOCK6: dedicator of cytokinesis 6; EOC: epithelial ovarian cancer; FIGO: Federation International of Gynecology and Obstetrics; G1: grade 1; G2: grade 2; G3: grade 3.

method. Multivariate Cox proportional hazards models were used to test the simultaneous effects of prognostic factors on survival. The hazard ratios (HR) and 95% confidence intervals (CI) were calculated. All statistical analyses were performed with SPSS v24 software. Graphs were prepared using GraphPad Prism 8.0. A *P*-value <0.05 was considered statistically significant. **P*<0.05; ***P*<0.01; ****P*< 0.001.

Results

Baseline characteristics of patients

The baseline characteristics of the sixty-five EOC patients were listed in **Table 1**. More than half of the patients (55.38%) were younger than fifty-five. When categorized by FIGO stage, 61.54% of patients were in stage III+IV. About half of the patients had high-grade (G3) EOC (64.62%), lymph node metastasis (46.15%) and were diagnosed with serous adenocarcinoma (43.08%). The majority of patients (93.85%) received surgery and adjuvant chemotherapy. After the primary surgery, the residual tumor of most patients (69.23%) was less than 1 cm.

DOCK6 expression in EOC tissues detected by IHC

We used IHC experiments to analyze the expression of DOCK6 in EOC tissues, including mesosalpinx cysts (**Figure 1A**), serous carcinoma (**Figure 1B**), endometrioid carcinoma (**Figure 1C**), clear cell carcinoma (**Figure 1D**) and mucinous carcinoma (**Figure 1E**). Immunoreactive DOCK6 was localized in the cytoplasm in all categories of EOC and 31/65 cases presented a high DOCK6 expression (IS≥5) (**Table 1**).

Correlation between the expression of DOCK6 and clinicopathological characteristics

The correlations between DOCK6 immunoreactivity and clinicopathological characteristics were analyzed by Pearson's χ^2 test or Fisher's exact test. Patients with FIGO III+IV stage had a significantly higher protein expression of DOCK6 when compared with that of patients with FIGO I+II EOC (P=0.01, **Figure 2A**). Furthermore, DOCK6 protein expression was significantly higher in high-grade EOC lesions, when compared to that of lesions with low-moderate grades (P=0.01, **Figure 2B**). However, we found no significant associations between the level of DOCK6 expression and patient age, lymph node metastasis, histological type, primary therapy or residual tumor (**Table 1**).

DOCK6 immunoreactivity and patient survival

DOCK6 expression, age, FIGO stage, tumor grade, lymph node metastasis, histologic type, primary therapy and residual tumor were evaluated as prognostic factors by Kaplan-Meier sur-

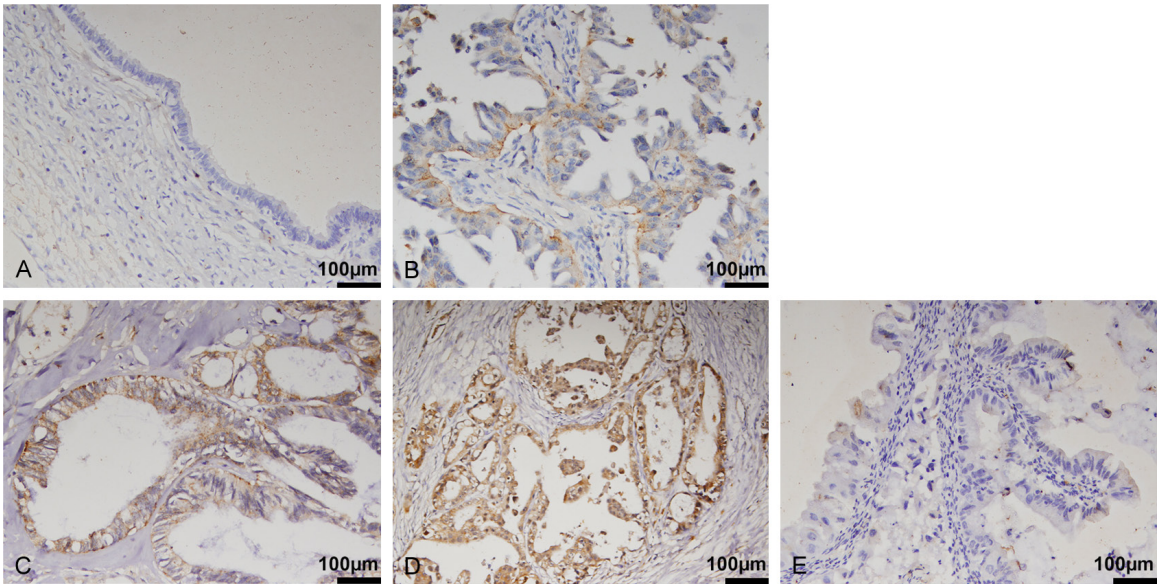

Figure 1. DOCK6 protein expression in EOC tissues (magnification, ×200). Mesosalpinx cysts tissue (A) was used as a negative control. The cases of EOC tissues were classified as serous carcinoma (B), endometrioid carcinoma (C), clear cell carcinoma (D) and mucinous carcinoma (E). Scale bar, 100 μm. DOCK6: dedicator of cytokinesis 6; EOC: epithelial ovarian cancer.

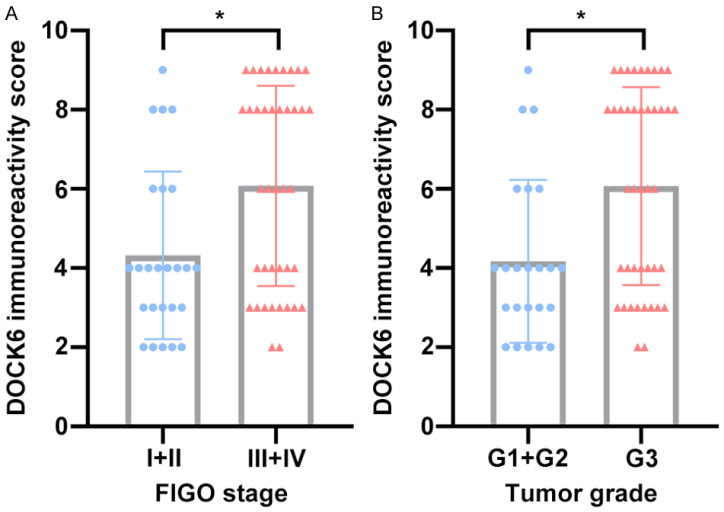

Figure 2. The expression of DOCK6 in EOC tissues grouped by clinicopathological parameters. (A) The expression of DOCK6 in FIGO I+II and FIGO III+IV stages. (B) The expression of DOCK6 in low-moderate (G1+G2) and high (G3) tumor grades. Blue circles (A): FIGO I+II stages; Red triangles (A): FIGO III+IV stages; Blue circles (B): low-moderate (G1+G2) tumor grades; Red triangles (B): high (G3) tumor grades; *: P<0.05; DOCK6: dedicator of cytokinesis 6; EOC: epithelial ovarian cancer; FIGO: Federation International of Gynecology and Obstetrics; G1: grade 1; G2: grade 2; G3: grade 3.

vival analysis. Among the 65 patients examined, 32 cases died of EOC and 33 cases were censored. Patients with a high expression of DOCK6 had poorer outcomes than those with a low expression of DOCK6 (P< 0.01, HR=3.34, 95% CI=1.65-6.79, **Figure 3A**). Moreover, FIGO III+IV stage (P<0.001, HR=31.80, 95% CI=15.90-63.60, **Figure 3B**), high tumor grade (P<0.001, HR= 5.62, 95% CI=2.80-11.28, **Figure 3C**), positive of lymph node metastasis (P<0.001, HR=11.26, 95% CI=5.37-23.62, **Figure 3D**), residual tumor ≥1 cm (P<0.001, HR= 6.74, 95% CI=2.73-16.68, **Figure 3E**) were associated with poor survival. However, there were no correlations between age, histologic type, primary therapy and the prognosis of EOC patients (**Table 2**).

The clinicopathological characteristics that were significant in univariate analysis, i.e. DOCK6 expression, FIGO stage, tumor grade, lymph node metastasis, residual tumor, were additionally investigated using multivariate Cox regression analysis. The results revealed that DOCK6 expression (P=0.04, HR=2.29, 95% CI=1.06-4.96), FIGO stage (P=0.02, HR=12.15, 95% CI=1.39-106.28) and residual tumor

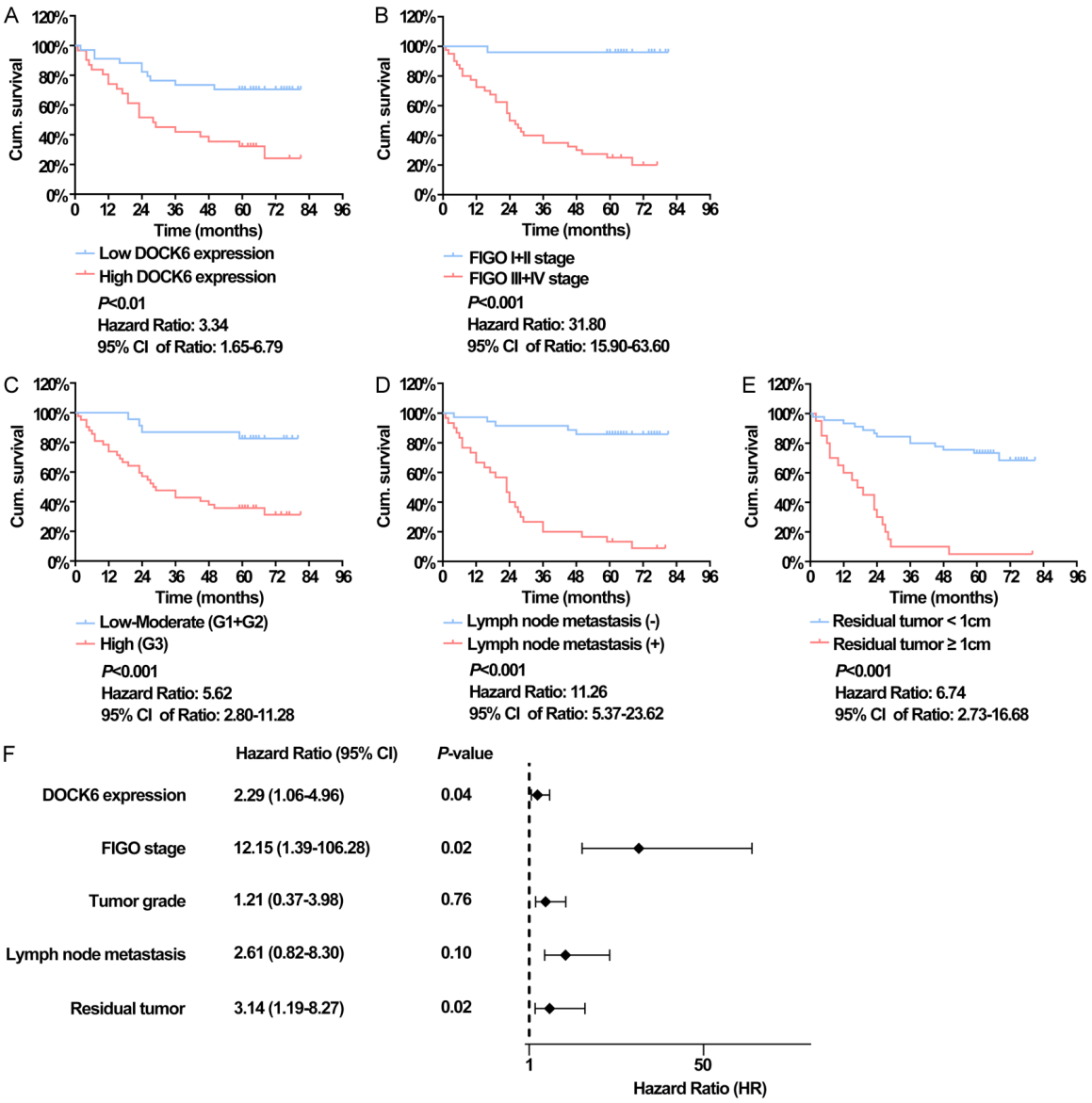

Figure 3. Survival curves of EOC patients based on clinicopathological parameters. A high expression of DOCK6 was found to be a poor prognostic factor of EOC patients using Kaplan-Meier analysis (P<0.01, A). Other clinical prognostic parameters were the FIGO stage (P<0.001, B), tumor grade (P<0.001, C), lymph node metastasis (P<0.001, D) and residual tumor (P<0.001, E). Prognostic values of clinicopathological parameters were shown by forest plot of hazard ratios using Multivariate Cox proportional hazards models (F). DOCK6: dedicator of cytokinesis 6; EOC: epithelial ovarian cancer; FIGO: Federation International of Gynecology and Obstetrics; G1: grade 1; G2: grade 2; G3: grade 3.

(P=0.02, HR=3.14, 95% CI=1.19-8.27) were independent prognostic factors (**Table 2**; **Figure 3F**).

Discussion

DOCK6, as an atypical Rho GEF, has been reported to promote vascular smooth muscle cell migration, axonal outgrowth and gastric cancer progression [24-27]. However, the role of DOCK6 in EOC is currently unknown. In the present study, the expression of DOCK6 in EOC tissues was examined. Furthermore, the correlation between clinicopathological characteristics was evaluated. These results suggested that DOCK6 is a novel independent prognostic biomarker of patients with EOC.

RAC1, CDC42 and RhoA belong to the Rho Family of GTPases and are involved in critical

Table 2. Univariate and multivariate analysis for the cumulative survival rate of EOC patients

Characteristics	N	Univariate analysis		Multivariate analysis	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age (years)		1.54 (0.76-3.12)	0.22		
≤55	36				
>55	29				
FIGO stage		31.80 (15.90-63.60)	<0.001	12.15 (1.39-106.28)	0.02
I+II	25				
III+IV	40				
Tumor grade		5.62 (2.80-11.28)	<0.001		
Low-Moderate (G1+G2)	23				
High (G3)	42				
Lymph node metastasis		11.26 (5.37-23.62)	<0.001		
Negative	35				
Positive	30				
Histologic type		0.67 (0.33-1.35)	0.25		
Serous adenocarcinoma	28				
Non-serous adenocarcinoma	37				
Primary therapy		0.76 (0.15-3.83)	0.71		
Surgery	4				
Surgery + Others	61				
Residual tumor		6.74 (2.73-16.68)	<0.001	3.14 (1.19-8.27)	0.02
<1 cm	45				
≥1 cm	20				
DOCK6 expression		3.34 (1.65-6.79)	<0.01	2.29 (1.06-4.96)	0.04
Low	34				
High	31				

DOCK6: dedicator of cytokinesis 6; EOC: epithelial ovarian cancer; FIGO: Federation International of Gynecology and Obstetrics; G1: grade 1; G2: grade 2; G3: grade 3.

cellular activities, such as actin polymerization, actin filament bundling, cell adhesion, cell polarity, endocytosis, vesicle trafficking, cancer metastasis and invasion [28-30]. These proteins have two conformational states: an active state bound to GTP and an inactive state bound to GDP. Rho GTPases are regulated by over 80 activators (GEFs) and over 70 inactivators (GTPase-activating proteins, GAPs) [31]. Rho GEFs transform GDP to GTP to generate their active forms, while the GAPs catalyze the opposite to inactivate the GTPase [32]. DOCK family GEFs are one class of Rho GEFs, involved in various human cancers and pathologies [33, 34]. Chang-Hwan *et al.* reported that the inhibition of Rac1 impaired the migration, invasion and malignant transformation of glioma stem-like cells [35]. Li *et al.* has shown a positive correlation between DOCK6 overexpression with gender, TNM stage and lymph node metastasis in gastric cancer. Furthermore, through the activation of RAC1 and CDC42, DOCK6 is able to induce the migration and invasion of gastric cancer cells [27]. Chi *et al.* also suggested that a positive DOCK6 expression of gastric cancer cells was associated with tumor size, lymph node metastasis and pathological stage [20]. The role of DOCK6 in EOC was in line with that of current research. In the present study, high DOCK6 expression in EOC tissues was positively associated with advanced FIGO stage, suggesting that DOCK6 may promote EOC progression via the DOCK6-RAC1/CDC42 axis. However, due to a lack of molecular experiments, the molecular mechanism of DOCK6 in EOC requires additional confirmation.

In our study, we found that DOCK6 expression, FIGO stage and residual tumor were associated with poor prognosis in EOC patients. FIGO stage and the size of the residual tumor are definitive factors affecting the overall survival rate of EOC

patients. In oral squamous cell cancer, Zhang et al. found that overexpression of DOCK6 promoted cellular migration and invasion and was associated with poor prognosis [36]. Earlier research reported that gastric cancer patients with positive DOCK6 expression presented shorter cumulative survival [20, 27]. These results were in consistent with DOCK6 being a novel independent prognostic factor for EOC.

Our study was retrospective in nature. Future prospective studies with larger-scale sample sizes are needed to validate the results presented here. In vivo and in vitro studies are required to address the biological roles and cell signaling pathways of DOCK6 in EOC.

Conclusion

In conclusion, the overexpression of DOCK6 on EOC tissues was associated with advanced FIGO clinical stage, indicating that DOCK6 may be involved in EOC progression. Furthermore, besides FIGO stage and residual tumor, our data validated DOCK6 expression as a novel independent prognostic marker for poor survival in EOC.

Acknowledgements

This study was supported by the National Key Research and Development Program of China, (2018YFC10022003), and Sichuan Science and Technology Program (2019YFH0081).

Disclosure of conflict of interest

None.

Address correspondence to: Shanling Liu, Department of Medical Genetics/Prenatal Diagnostic Center, West China Second University Hospital, No. 20, Section 3, Renminnan Road, Chengdu 610041, Sichuan, China. E-mail: sunny630@126.com

References

[1] Erickson BK, Conner MG and Landen CN Jr. The role of the fallopian tube in the origin of ovarian cancer. Am J Obstet Gynecol 2013; 209: 409-414.

[2] Han GYQ, Alexander M, Gattozzi J, Day M, Kirsch E, Tafreshi N, Chalar R, Rahni S, Gossner G, Burke W and Damaghi M. Ecological and evolutionary dynamics to design and improve ovarian cancer treatment. Clin Transl Med 2024; 14: e70012.

[3] Malek Mohammadi M, Rismanchi H, Esmailzadeh S, Farahani A, Hedayati N, Alimohammadi M, Mafi A, Farahani N and Hushmandi K. The emerging role of circular RNAs in cisplatin resistance in ovarian cancer: from molecular mechanism to future potential. Noncoding RNA Res 2024; 9: 1280-1291.

[4] Komiyama S, Katabuchi H, Mikami M, Nagase S, Okamoto A, Ito K, Morishige K, Suzuki N, Kaneuchi M, Yaegashi N, Udagawa Y and Yoshikawa H. Japan Society of Gynecologic Oncology guidelines 2015 for the treatment of ovarian cancer including primary peritoneal cancer and fallopian tube cancer. Int J Clin Oncol 2016; 21: 435-446.

[5] Wu X, Liu J, An R, Yin R, Zhang Y, Zhou H, He A, Wang L, Zhang J, Liu Z, Duan W, Zhu J, Lou G, Chen G, Cheng Y, Xue F, Nick S, Wang H and Li D. First-line bevacizumab plus chemotherapy in Chinese patients with stage III/IV epithelial ovarian cancer, fallopian tube cancer or primary peritoneal cancer: a phase III randomized controlled trial. J Gynecol Oncol 2024; 35: e99.

[6] Kukimoto-Niino M, Katsura K, Ishizuka-Katsura Y, Mishima-Tsumagari C, Yonemochi M, Inoue M, Nakagawa R, Kaushik R, Zhang KYJ and Shirouzu M. RhoG facilitates a conformational transition in the guanine nucleotide exchange factor complex DOCK5/ELMO1 to an open state. J Biol Chem 2024; 300: 107459.

[7] Roy D, Sengupta D and Kulkarni K. Substrate induced dynamical remodeling of the binding pocket generates GTPase specificity in DOCK family of guanine nucleotide exchange factors. Biochem Biophys Res Commun 2022; 631: 32-40.

[8] Kukimoto-Niino M, Ihara K, Murayama K and Shirouzu M. Structural insights into the small GTPase specificity of the DOCK guanine nucleotide exchange factors. Curr Opin Struct Biol 2021; 71: 249-258.

[9] Gadea G and Blangy A. Dock-family exchange factors in cell migration and disease. Eur J Cell Biol 2014; 93: 466-477.

[10] Miyamoto Y, Yamauchi J, Sanbe A and Tanoue A. Dock6, a Dock-C subfamily guanine nucleotide exchanger, has the dual specificity for Rac1 and Cdc42 and regulates neurite outgrowth. Exp Cell Res 2007; 313: 791-804.

[11] Dudoignon B, Huber C, Michot C, Di Rocco F, Girard M, Lyonnet S, Rio M, Rabia SH, Daire VC and Baujat G. Expanding the phenotype in Adams-Oliver syndrome correlating with the genotype. Am J Med Genet A 2020; 182: 29-37.

[12] Nieto-Benito LM, Suárez-Fernández R and Campos-Domínguez M. A novel pathogenic variation of DOCK6 gene: the genotype-pheno-

type correlation in Adams-Oliver syndrome. Mol Biol Rep 2023; 50: 5519-5521.
[13] Zepeda-Romero LC, Zenker M, Schanze D, Schanze I, Peña-Padilla C, Quezada-Salazar CA, Pacheco-Torres PA, Rivera-Montellano ML, Aguirre-Guillén RL, Bobadilla-Morales L, Corona-Rivera A and Corona-Rivera JR. Intrafamilial phenotypic variability in autosomal recessive DOCK6-related Adams-Oliver syndrome. Eur J Med Genet 2022; 65: 104653.
[14] Yoshitomi M, Tsujimoto SI, Ikeda J, Kawai T, Ohki K, Hara Y, Yamato G, Tanoshima R, Tomizawa D, Shimada A, Horibe K, Adachi S, Taga T, Tawa A, Hayashi Y, Ito S and Shiba N. High DOCK1 expression identifies a distinct prognostic subgroup of pediatric acute myeloid leukemia: results of the Japanese pediatric leukemia/lymphoma study group AML-05 trial. Pediatr Blood Cancer 2024; 71: e31151.
[15] Xie S, Jin Y, Wang J, Li J, Peng M and Zhu X. DOCK1 regulates the malignant biological behavior of endometrial cancer through c-Raf/ERK pathway. BMC Cancer 2024; 24: 296.
[16] Galloni C, Egnuni T, Zahed Mohajerani S, Ye J, Mittnacht S, Speirs V, Lorger M and Mavria G. Brain endothelial cells promote breast cancer cell extravasation to the brain via EGFR-DOCK4-RAC1 signalling. Commun Biol 2024; 7: 602.
[17] Chen W, Zhou M, Guan B, Xie B, Liu Y, He J, Zhao J, Zhao Q and Yan D. Tumour-associated macrophage-derived DOCK7-enriched extracellular vesicles drive tumour metastasis in colorectal cancer via the RAC1/ABCA1 axis. Clin Transl Med 2024; 14: e1591.
[18] Gutierrez-Ruiz OL, Johnson KM, Krueger EW, Nooren RE, Cruz-Reyes N, Heppelmann CJ, Hogenson TL, Fernandez-Zapico ME, McNiven MA and Razidlo GL. Ectopic expression of DOCK8 regulates lysosome-mediated pancreatic tumor cell invasion. Cell Rep 2023; 42: 113042.
[19] Zhang L, Cao Y, Dai X and Zhang X. Deciphering the role of DOCK8 in tumorigenesis by regulating immunity and the application of nanotechnology in DOCK8 deficiency therapy. Front Pharmacol 2022; 13: 1065029.
[20] Chi HC, Tsai CY, Wang CS, Yang HY, Lo CH, Wang WJ, Lee KF, Lai LY, Hong JH, Chang YF, Tsai MM, Yeh CT, Wu CH, Hsieh CC, Wang LH, Chen WJ and Lin KH. DOCK6 promotes chemo- and radioresistance of gastric cancer by modulating WNT/beta-catenin signaling and cancer stem cell traits. Oncogene 2020; 39: 5933-5949.
[21] Mutch DG and Prat J. 2014 FIGO staging for ovarian, fallopian tube and peritoneal cancer. Gynecol Oncol 2014; 133: 401-404.
[22] Zhou J, Jiang W, Huang W, Ye M and Zhu X. Prognostic values of transforming growth factor-beta subtypes in ovarian cancer. Biomed Res Int 2020; 2020: 2170606.
[23] Zhang J, Liu XH, Li C, Wu XX, Chen YL, Li WW, Li X, Gong F, Tang Q and Jiang D. SNCG promotes the progression and metastasis of high-grade serous ovarian cancer via targeting the PI3K/AKT signaling pathway. J Exp Clin Cancer Res 2020; 39: 79.
[24] Miyamoto Y, Torii T, Yamamori N, Ogata T, Tanoue A and Yamauchi J. Akt and PP2A reciprocally regulate the guanine nucleotide exchange factor Dock6 to control axon growth of sensory neurons. Sci Signal 2013; 6: ra15.
[25] Shi L. Dock protein family in brain development and neurological disease. Commun Integr Biol 2013; 6: e26839.
[26] Kim K, Yang DK, Kim S and Kang H. miR-142-3p is a regulator of the TGFβ-mediated vascular smooth muscle cell phenotype. J Cell Biochem 2015; 116: 2325-2333.
[27] Li X, Jiang M, Chen D, Xu B, Wang R, Chu Y, Wang W, Zhou L, Lei Z, Nie Y, Fan D, Shang Y, Wu K and Liang J. miR-148b-3p inhibits gastric cancer metastasis by inhibiting the Dock6/Rac1/Cdc42 axis. J Exp Clin Cancer Res 2018; 37: 71.
[28] Burridge K and Wennerberg K. Rho and rac take center stage. Cell 2004; 116: 167-179.
[29] Orgaz JL, Herraiz C and Sanz-Moreno V. Rho GTPases modulate malignant transformation of tumor cells. Small GTPases 2014; 5: e29019.
[30] Kazanietz MG and Caloca MJ. The rac GTPase in cancer: from old concepts to new paradigms. Cancer Res 2017; 77: 5445-5451.
[31] Sadok A and Marshall CJ. Rho GTPases: masters of cell migration. Small GTPases 2014; 5: e29710.
[32] Rossman KL, Der CJ and Sondek J. GEF means go: turning on RHO GTPases with guanine nucleotide-exchange factors. Nat Rev Mol Cell Biol 2005; 6: 167-180.
[33] Laurin M and Cote JF. Insights into the biological functions of Dock family guanine nucleotide exchange factors. Genes Dev 2014; 28: 533-547.
[34] Nishikimi A, Kukimoto-Niino M, Yokoyama S and Fukui Y. Immune regulatory functions of DOCK family proteins in health and disease. Exp Cell Res 2013; 319: 2343-2349.
[35] Yoon CH, Hyun KH, Kim RK, Lee H, Lim EJ, Chung HY, An S, Park MJ, Suh Y, Kim MJ and Lee SJ. The small GTPase Rac1 is involved in the maintenance of stemness and malignancies in glioma stem-like cells. FEBS Lett 2011; 585: 2331-2338.
[36] Zhang ZY, Sun YY, Wang HC, Fu WN and Sun CF. Overexpression of DOCK6 in oral squamous cell cancer promotes cellular migration and invasion and is associated with poor prognosis. Arch Oral Biol 2022; 133: 105297.