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Original Article

Expression of kinesin family member 3B is associated with poor prognosis in epithelial ovarian cancer patients

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Abstract: Kinesin family member 3B (KIF3B) has been identified as a prognostic biomarker for a variety of human cancers. We investigate the clinically relevant of KIF3B expression and its functional role in EOC. Nine fresh frozen ovarian tissues were evaluated the expression of KIF3B by western blot analysis. The 119 cases of ovarian tumors were performed by immunohistochemical analysis, it was related to the histological grade (P = 0.046), peritoneal fluid (P = 0.040), malignant cell of peritoneal fluid (P = 0.008), and metastasis (P = 0.016), according to the International Federation of Gynecology and Obstetrics classification. Kaplan-Meier analysis revealed that patients with KIF3B expression had shorter progression-free survival among all the patients (P = 0.001) and in particular between patients with advanced stages (P = 0.009). Meanwhile, following release of EOC cell HO8910 from serum starvation, the expression of KIF3B was up-regulated; this means that KIF3B can promote the proliferation of EOC cell HO8910 in the cell cycle. Therefore, these findings suggested that KIF3B expression may play an important role in tumor progression into advanced stage with poor prognosis in EOC and down-regulation of KIF3B on tumor cells may be a therapeutic target in those patients.

Keywords: Epithelial ovarian cancer, kinesin family member 3b, molecular target, prognosis

Introduction

Epithelial ovarian cancer (EOC) is the second most common gynecological cancer and the leading reason of cancer death in women in the industrialized world [1, 2], it is a common malignant ovarian neoplasm with poor five-year survival rate (less than 30%) without effective early diagnostic methods [3-5], even after comprehensive therapies like surgical excision, chemotherapy, and radiotherapy. What is more, this tumor shows a high percentage of recurrence and metastasis [6, 7]. A single approach to therapy scheme is unlikely to achieve similar success across all patients. Therefore, investigation into the molecules that contribute to progression and metastasis of ovarian tumors is urgently needed.

Kinesins super-family proteins (KIFs) were found for the first time in 1985, Which are composed of molecular motors that transport intracellular cargo and orchestrates a variety of cellular processes along microtubules using the energy derived from ATP hydrolysis [8-15]. Bioinformatics approaches have described that, in mammals, KIFs could regulate and change almost 50% of the protein-coding genes [16], that have been related to the pathogenesis of several human diseases [17]. They also associated with a variety of cellular processes, including the mitosis and meiosis of the cell, and macromolecular transport between the cells. The mitosis is a highly regulated process in eukaryotic cell division. Any abnormal mitotic process will lead to gene additions, deletions or substitutions, leading to cell abnormalities or apoptosis [8, 9, 18].

Kinesin family member 3B (KIF3B) is a member of the kinesin super-family proteins. There are at least seven members in this super-family, namely, KIFlA, KIFlB, KIF2, KIF3A, KIF3B, KIF4, and KIF5 [19]. KIF3B was expressed predomi-

Table 1. KIF3B expression and clinicopathological parameters in 119 ovarian cancer specimens

Clinicopathological parameters		KIF3B Expression		P
		Low	High	
Age, yr				0.840
≤50	35	13	22	
>50	84	27	57	
Menopausal state, n (%)				0.702
No	43	20	23	
Yes	76	32	44	
FIGO stage, n (%)				0.132
I	52	17	35	
II	13	1	12	
III	49	20	29	
IV	5	2	3	
Histological grade, n (%)				0.046*
1	7	6	1	
2	36	11	25	
3	76	23	53	
Histological subtype, n (%)				0.144*
Serous	61	19	42	
Mucinous	5	2	3	
Endometrioid	10	5	5	
Clear cell	10	3	7	
Others	33	10	23	
Lymph node status, n (%)				0.361
Negative	96	33	63	
Positive	23	8	15	
Peritoneal fluid, n (%)				0.040*
Absent	72	26	46	
Present	47	15	32	
Malignant tumor cells in peritoneal fluid, n (%)				0.008*
Absent	91	31	60	
Present	28	9	19	
Other organ metastasis, n (%)				0.016*
Absent	60	27	33	
Present	59	16	43	
Ki67				0.046*
Low expression	33	19	14	
High expression	86	33	53	

*Statistical analyses were performed by the Pearson χ^2 test. P<0.05 was considered significant.

nantly in neural tissues, and involved in a wide range of biological processes, such as vesicle transport and membrane expansion during mitosis through targeting of other molecules [19-22]. It has been reported that KIF3B plays an important role in cervical cancer and hepatocellular carcinoma, especially in tumor development, progression and proliferation [18, 23], Therefore, through the above background information, we sought to investigate the expression and function of KIF3B in EOC. We examined the expression of KIF3B in EOC tissue specimens by immunohistochemistry, and evaluated the prognostic value of KIF3B in EOC patients by survival analysis, then investigated the possible effects of KIF3B on EOC cell proliferation by serum starvation release.

Materials and methods

Tissue samples

There are 119 paraffin-embedded sections from patients who underwent surgery between 2004 and 2009 obtained from the Department of Pathology at Affiliated Hospital of Nantong University. All human tissues were collected using protocols approved by the Ethics Committee of Affiliated Hospital of Nantong University. The cases were reviewed and classified by gynecologic pathologists using histological criteria described previously [16, 24], and all cases were validated by morphologic review at the time of retrieval. Fresh samples were frozen in the ice immediately after surgical removal and maintained at -80°C until used for Western blot analysis. The clinical features of the patients, including age, FIGO stage, histological grade, histological subtype, lymph node status, peritoneal fluid, malignant tumor cell in peritoneal fluid, other organ metastasis were shown in **Table 1**.

Antibodies

The antibodies used for Western blotting and immunohistochemistry in this study included: anti-human KIF3B antibody (diluted 1:1000 used in Western blot, and 1:300 used in immunohistochemical staining), anti-human Ki67 antibody (1:500 used in Western blot), anti-human GAPDH antibody (1:1000 used in Western blot), anti-human CDK2 antibody (1:1000 used in Western blot) and anti-human cyclins A antibody (1:1000 used in Western blot). All the antibodies were obtained from Santa Cruz Biotechnology, USA.

Western blot analysis

Western blot analysis was performed as described earlier [25]. Briefly, 40 mg total protein

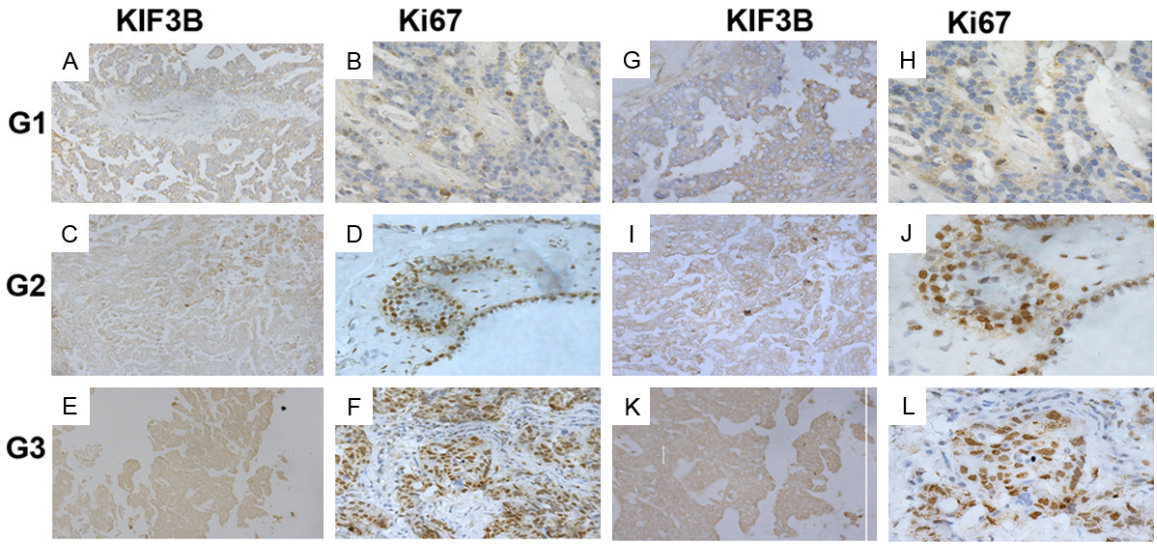

Figure 1. Immunohistochemical staining analysis in Paraffin-embedded EOC tissues. A-L. The tissue sections were stained with antibodies of KIF3B and Ki67 and counterstained with hematoxylin. A, B, G, H. Histological differentiation grade 1. C, D, I, J. Histological differentiation grade 2. E, F, K, L. Histological differentiation grade 3. The experiment details were described in section materials and methods. Magnification ×200 and ×400.

extracts were separated with SDS-polyacrylamide gel electrophoresis (SDS PAGE) and transferred to polyvinylidene difluoride filter (PVDF) membranes (Immbilon; Millipore). The membranes were blocked with the milk. Then, the membranes immunoreactive bands were visualized by chemiluminescence detection system (Pierce), then, the band density was measured with a computer assisted image analysis system (Adobe Systems, San Jose, CA, USA). Band densities were measured for at least three independent reactions.

Immunohistochemical staining

Briefly, immunohistochemical staining was performed with the standard peroxidase/DAB method on paraffin-embedded tissue sections. KIF3B expression was detected by rabbit anti-KIF3B antibody. Immunohistochemical procedures were performed as described previously [26]. According to the manufacturer's protocol, tissue sections were lightly counterstained with hematoxylin, examined by light microscopy. Two pathologists blindly reviewed specimen and evaluated the immunohistochemical staining without knowledge of the clinical outcome. For authentication of KIF3B and Ki67, high-power fields in each specimen were selected by random independent, and nuclear staining of Ki67 was examined under high magnification vision. More than 200 cells were counted to determine the mean percent, which represented the percentage of immunostained cells related to the total number of cells. In half of the samples, staining was repeated twice to avoid possible technical errors, but similar results were obtained in these tissue samples. Using light microscopy, two investigators (RL and SY), who were blinded to patients' data, interpreted immunostaining results. The locations of immunoreactivity (epithelia, membrane, stroma and nuclear) were noted. Percentage of stained cells was noted as rare, <25% (0), 25-75% (1) and >75% (2). Immunostaining intensity was reported as absent (0), weak (1), moderate (2), or strong (3). Staining index (SI) was calculated as the product of staining intensity score and the proportion of positive tumor cells. Using this method of assessment, we evaluated KIF3B expression in EOC by determining the SI. And SI score of ≥4 was used to define tumors with high KIF3B expression, and an SI score of ≤3 was used to indicate low KIF3B expression A third investigator (JL) reviewed any discrepancies in the interpretation of the immunostaining results and rendered a final diagnosis [27, 28].

Cell lines cultures and cell cycle analysis

The human EOC cell lines HO8910, OVCAR, SKOV3 and A2780 was cultured in RPMI 1640 supplemented with 10% foetal bovine serum, 100 U/ml penicillin and 100 μg/ml streptomy-

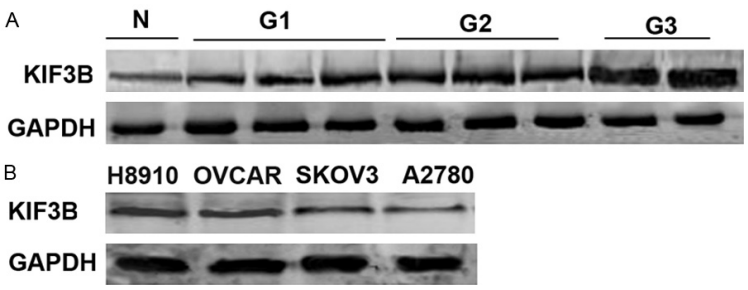

Figure 2. Expression of KIF3B is high in EOC. A. Western blot of 1 normal ovarian tissue (N) and 8 EOC tissues (histological differentiation grade 1 G1, grade 2 G2 and grade 3 G3) showed that the KIF3B expression was significantly higher in tumorous tissues than in normal tissues. B. KIF3B expression was increased in EOC cell lines including HO8910, OVCAR, SKOV3 and A2780 by western blot. GAPDH was used as a control for protein load and integrity.

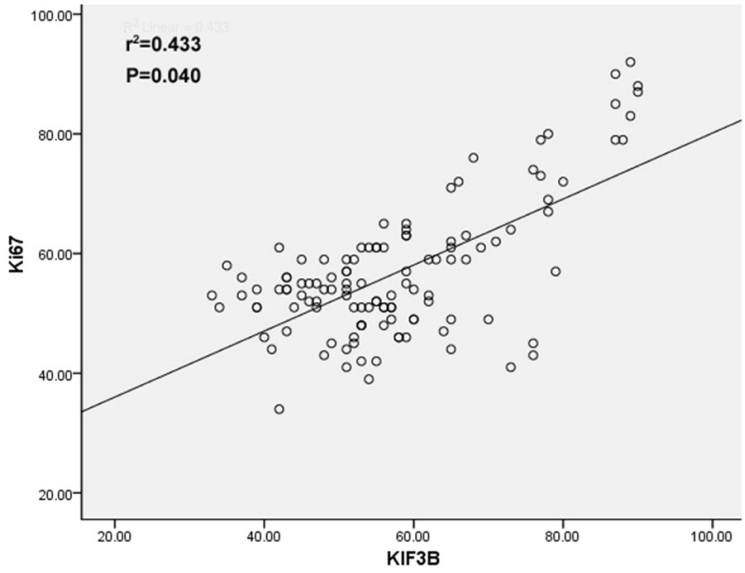

Figure 3. Relationship between KIF3B and Ki67 proliferation index expression in EOC. Scatter-plot of KIF3B versus Ki67 with regression line showed a correlation of them using the Pearson's correlation co-efficient.

cin (all from Invitrogen, Carlsbad, CA, USA) at 37°C in an atmosphere of 5% CO_2 in air. HO8910 cells were subjected to serum starvation for 36 h. Then, cells were harvested at 0, 4, 8, 12 and 24 h and saved with 70% ice-cold ethanol at 4°C for cell cycle analyses, and then incubated with 1 mg/ml RNase A for 20 min. Subsequently, cells were stained with propidium iodide (PI, 50 mg/ml, Becton-Dickinson, San Jose, CA, USA) in PBS-Triton×100, and the number of cells in the cell cycle was analyzed with a Becton-Dickinson flow cytometer BD FACScan (San Jose, CA) [29]. Gating was set to exclude cell debris, cell doublets, and cell clumps.

Statistical analysis

Statistical analysis was performed using the PASW statistics 19 software package. The statistical significance of the correlations between Kif3B expression and the clinicopathologic features were analyzed using the X^2-test. Overall survival curves were calculated with the Kaplan-Meier method and were analyzed with the log-rank test. The values were expressed as mean ± SD, and $P < 0.05$ was considered statistically significant.

Results

KIF3B is expressed at high levels in EOC

To analyze the expression levels of the KIF3B protein in EOC tissues, 119 tissue samples including 61 serous, 10 endometrioid, 10 clear cell, 10 mucinous subtypes and 33 other subtypes from EOC patients who received postoperative platinum-based chemotherapy were examined by immunohistochemistry, and KIF3B expressions were scored as positive when strong cytoplasm, occasionally within the cytoplasm as punctuated staining. Representative examples of reactivity for KIF3B and Ki67 are shown in **Figure 1**. We were interested in the expression status of KIF3B in EOC fresh tissues, thus western blotting analysis was performed to measure KIF3B protein level. In **Figure 2A**, the expression of KIF3B was high in cancer tissues, and low in normal tissues. Meanwhile, we investigated the expression of KIF3B in human EOC cell lines including HO8910, OVCAR, SKOV3 and A2780 by western blot. KIF3B was expressed in the EOC cell lines. Based on this result as showed in **Figure 2B**, we decided to use HO8910, which highly express KIF3B, to evaluate the efficacy of KIF3B on cell proliferation.

Table 2. Survival status and clinicopathological parameters in 119 human ovarian cancer specimens

Clinicopathological parameters	Total	Survival Status		P
		Alive	Dead	
Age, yr				0.103
≤50	35	21	14	
>50	84	52	32	
FIGO stage, n (%)				<0.001*
I	52	30	22	
II	13	12	1	
III	49	27	22	
IV	5	3	2	
Histological grade, n (%)				0.007*
1	7	1	6	
2	36	22	14	
3	76	50	26	
Histological subtype, n (%)				0.026*
Serous	61	39	22	
Mucinous	5	2	3	
Endometrioid	10	7	3	
Clear cell	10	4	6	
Others	33	21	12	
Lymph node status, n (%)				0.103
Negative	96	58	38	
Positive	23	15	8	
Peritoneal fluid, n (%)				0.345
Absent	72	43	29	
Present	47	30	17	
Malignant tumor cells in peritoneal fluid, n (%)				0.127
Absent	91	55	36	
Present	28	18	10	
Other organ metastasis, n (%)				<0.001*
Absent	60	33	27	
Present	59	40	19	
KIF3B				0.025*
Low expression	46	25	21	
High expression	73	25	48	
Ki67				0.040*
Low expression	33	19	14	
High expression	86	21	55	

*Statistical analyses were performed by the Pearson χ^2 test. P<0.05 was considered significant.

Correlation between KIF3B expression and clinic pathological parameters in EOC

To further explore the physiological and pathological relationship between the expression of KIF3B and Ki67 in EOC, the presence of KIF3B in different grade and histological types is summarized in **Table 1**. KIF3B had a higher expression in poor differentiated specimens compared with well-differentiated groups. It was found that KIF3B expression was significantly associated with the histological grade (P = 0.046), peritoneal fluid (P = 0.040), malignant cell of peritoneal fluid (P = 0.008) and metastasis (P = 0.016). But there was no correlation with age (P = 0.840), FIGO stage (P = 0.132), histological subtype (P = 0.144), lymph node status (P = 0.361). Besides, the scatterplot of KIF3B versus Ki67 with regression line showing a correlation of them by the Pearson's correlation co-efficient. We found that there was a positive correlation between KIF3B expression and Ki67-based proliferative activity (r^2 = 0.433, r = 0.658, P = 0.040; **Figure 3**).

KIF3B was significantly associated with the prognosis of EOC patients

To determine whether KIF3B is a prognostic factor in EOC, univariate analysis was showed that FIGO stage (P<0.001), histological grade (P = 0.007), histological subtype (P = 0.026), other organ metastasis (P<0.001), and Ki67 (P = 0.040) significantly influenced survival (**Table 2**). Patients with high KIF3B expression had a poor progression-free survival (PFS) of the patients than those with low KIF3B expression (P = 0.001) **Figure 4A**. KIF3B expression predicted PFS, when confined to patients with advanced stage (n = 54), the high expression of KIF3B significantly predicted PFS (P = 0.009; **Figure 4B**). In a word, KIF3B expression showed was a prognostic factor for patients' overall survival (**Table 2**; **Figure 4**). Multivariate analysis using the Cox's proportional hazards model revealed that age (P = 0.011), KIF3B expression (P = 0.047), and Ki-67 expression (P = 0.044) were prognostic indicators of overall survival (**Table 3**).

KIF3B was related to the proliferation of HO8910 cells

The western blot and immunohistochemistry results in EOC indicated that the expression of KIF3B might relate to progression of EOC. We proposed that KIF3B might have an effect on cell cycle progress of EOC cells. We investigated the expression of KIF3B during serum starvation and refeeding process. KIF3B content was significantly increased upon serum addition by Western blot (**Figure 5**). The expression

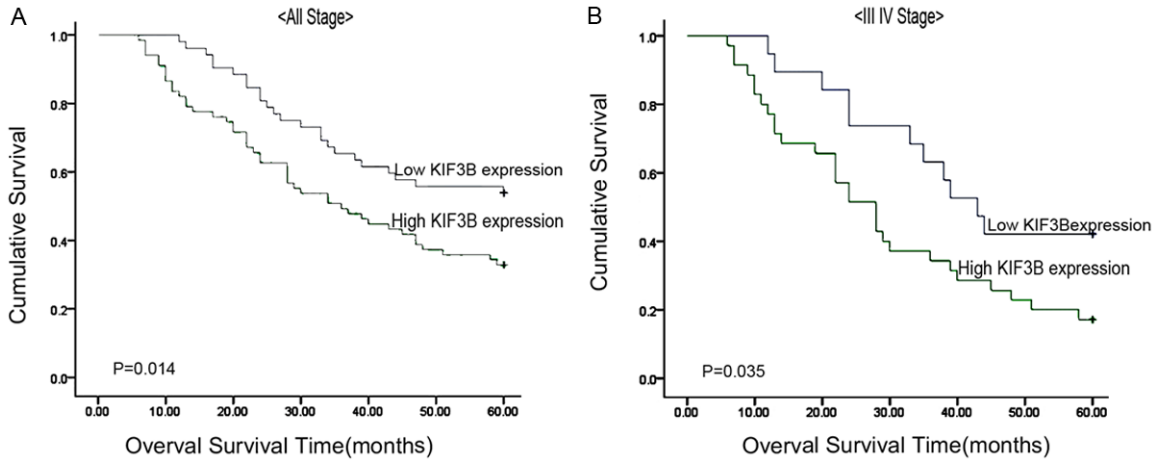

Figure 4. Progression-free survival curves of patients according to the expression of KIF3B (A) in 119 patients with all stages and (B) in 54 patients with stages III and IV EOC, patients in the high KIF3B expression grade group had significantly shorter overall survival.

Table 3. Contribution of various potential prognostic factors to survival by Cox regression analysis on 119 human ovarian cancer specimens

	Hazard ratio	P	95.0% Confidence interval
Age	2.161	0.011*	1.197-3.901
FIGO stage	1.537	0.034*	1.033-2.287
Histological grade	1.678	0.057	0.984-2.286
Histological subtype	0.963	0.627	0.827-1.121
Lymph node status	1.150	0.637	0.644-2.053
Peritoneal fluid	0.765	0.465	0.372-1.571
Malignant tumor cells in peritoneal fluid	1.417	0.394	0.636-3.156
Other organ metastasis	1.142	0.744	0.515-2.533
KIF3B expression	1.740	0.047*	1.006-3.010
Ki-67 expression	1.881	0.044*	1.018-3.476

Statistical analyses were performed by the Cox regression analysis. *P<0.05 was considered significant.

of cell proliferation markers such as cyclins A and cyclin-dependent kinases 2 (CDK2) was also increased after the serum refeeding. Thus, these results indicated that the expression of KIF3B might impact the proliferation of HO8910 cells.

Discussion

Kinesin superfamily members play a very important role in numerous cellular processes including intracellular transportation and cell division [9]. Studies have shown that the expression and function of Kinesin superfamily members play a key role in the development or progression of many kinds of human diseases, containing human hepatocellular carcinoma, ovarian cancer, cervical cancer [18, 23, 30, 31].

We first provide biological relevance to KIF3B as a potential oncogene in ovarian cancer. That is a protein highly expressed in EOC specimens and correlate with histological differentiation and clinical stage of EOC. Statistical data analysis indicated that KIF3B could be an independent prognostic factor for the survival of EOC patients. These findings supported the hypothesis that KIF3B could be an important regulator and prognostic factor for EOC. In summary, we found KIF3B to be frequently expressed in EOC tissues **Figure 2**. KIF3B expressions were marked as positive when strong cytoplasm. Representative examples of reactivity for KIF3B and Ki67 are shown in **Figure 1**. There was a positive correlation between KIF3B expression and Ki67-based proliferative activity, as showed in **Figure 3**. We also found that KIF3B expression was significantly associated with the histological grade (P = 0.046), peritoneal fluid (P = 0.040), malignant cell of peritoneal fluid (P = 0.008), and metastasis (P = 0.016) (**Table 1**). Our preliminary survival analysis indicated that high KIF3B expression might be associated with inferior

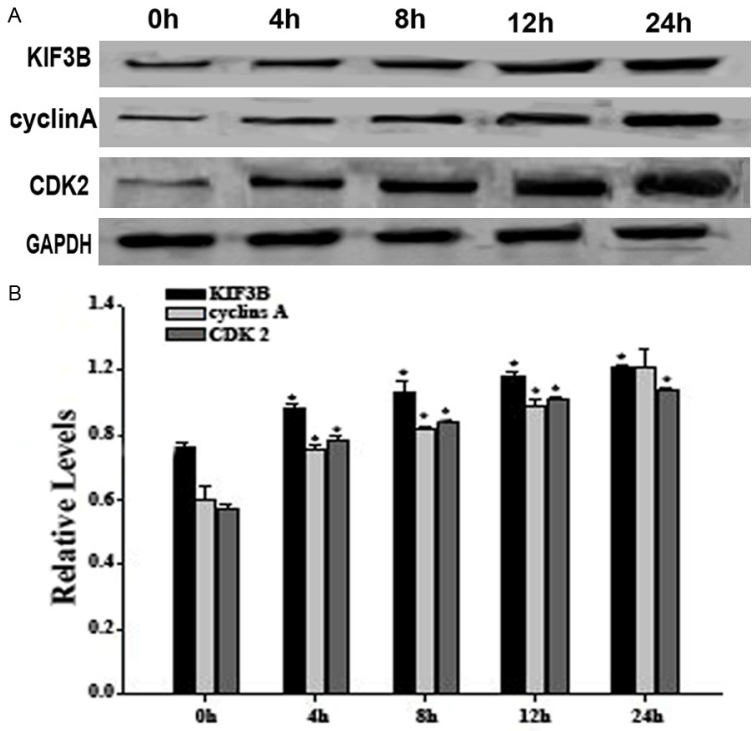

Figure 5. Expression of KIF3B and cell cycle related molecules were detected in proliferating HO8910 cells. A. A representative western blot image showed that the expression of KIF3B, cyclins A, and CDK2 in HO8910 cells that were subjected to serum starvation for 36 h and refeeding for 0, 4, 8, 12 and 24 h. GAPDH was used as a control for protein load and integrity. B. A bar chart demonstrated the relative protein expression of KIF3B, cyclins A, and CDK 2 in HO8970 cells at different time points, as measured by Western blot analysis. Data are presented as mean ± SEM of 3 independent measurements (*P<0.05 compared with control: 0 h).

overall survival, especially in people with advanced EOC (**Figure 3**).

Further study confirmed the potential role of KIF3B in EOC cell proliferation. We detected the expression of KIF3B during cell-cycle progression in HO8910 cells, and found that the protein expression of KIF3B was increased during the G1- to S-phase transition. We also examined the expression of cyclins A and CDK2 which were increased during cell-cycle progression through triggering the G2/M transition [32]. The expression of KIF3B was consistent with them during the cell cycle. Thus, the results showed that the expression of KIF3B might impact the proliferation of EOC cells (**Figure 4**).

In summary, our studies support a novel role for KIF3B in cell proliferation. From these data, we can expect that expression of KIF3B might potentially be an effective therapeutic approach for the inhibition of cell proliferation of EOC. Therefore, KIF3B may serve as a novel molecular target for the detection and treatment of EOC and other human cancers.

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Disclosure of conflict of interest

None.

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