

The expression of MAP4K4 and HIF2 α in peripheral blood of patients with locally advanced cervical cancer is correlated with excessive activation of autophagy and sensitivity to platinum-based neoadjuvant chemotherapy

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Abstract: Objective: To investigate the expression of mitogen-activated protein kinase kinase kinase kinase-4 (MAP4K4) and Hypoxia-inducible factor 2 α (hypoxia-inducible factor 2 α) in peripheral blood of patients with locally advanced cervical cancer. The relationship between the expression of HIF 2 α and the over-activation of autophagy and sensitivity to platinum-based neoadjuvant chemotherapy in cervical cancer patients. Methods: A total of 230 patients with locally advanced cervical cancer admitted to our hospital from August 2022 to August 2025 were prospectively selected as the research objects. The expressions of MAP4K4, HIF2 α and autophagy-related genes [LC-3II, LC-3I and Beclin-1] in peripheral blood before and after chemotherapy were detected by qRT-PCR. Pearson test was used for correlation analysis. Logistic regression model was used to analyze the independent risk factors of chemotherapy sensitivity. Results: MAP4K4 and HIF2 α were expressed in peripheral blood of patients with locally advanced cervical cancer in the subgroups of age, tumor size and histological type ($P > 0.05$), while MAP4K4 and HIF2 α were expressed in the subgroups of differentiation, FIGO stage and lymph node metastasis ($P < 0.05$). Before chemotherapy, MAP4K4 mRNA and HIF2 α mRNA in peripheral blood were compared between the two groups ($P > 0.05$). After chemotherapy, two groups of MAP4K4 mRNA, HIF2 alpha mRNA were significantly lower ($P < 0.05$), and effective group MAP4K4 mRNA, HIF2 alpha mRNA significantly below invalid group ($P < 0.05$); Before chemotherapy, LC-3II, LC-3I and Beclin-1 were compared between the two groups ($P > 0.05$); After chemotherapy, LC-3II, LC-3I and Beclin-1 in the two groups were increased, and LC-3II, LC-3I and Beclin-1 in the ineffective group were significantly higher than those in the effective group ($P < 0.05$). MAP4K4 and HIF2 α were positively correlated with LC-3II, LC-3I and Beclin-1 ($P < 0.05$). The degree of differentiation, FIGO stage, lymph node metastasis, LC-3II, LC-3I, Beclin-1, MAP4K4 and HIF2 α were independent risk factors for chemotherapy sensitivity in patients with locally advanced cervical cancer ($P < 0.05$). Conclusions: MAP4K4 and HIF2 α are up-regulated in patients with locally advanced cervical cancer, which are closely related to the excessive activation of autophagy during chemotherapy and the sensitivity to platinum-based neoadjuvant chemotherapy.

Keywords: Locally advanced cervical cancer; MAP4K4; HIF2 α ; Excessive activation of autophagy; Sensitivity to platinum-based neoadjuvant chemotherapy

Cervical cancer is a major public health problem worldwide. It is a common malignant tumor^[1] of the female reproductive system. Epidemiological studies have shown^[2] that the incidence of cervical cancer is second only to breast cancer, and the affected population tends to be younger in recent years. Surgery is the main treatment for early-stage cervical cancer, which can effectively eradicate the disease and improve the prognosis of patients. Patients with locally advanced cervical cancer are mostly treated with concurrent chemoradiotherapy to delay the progression of the disease. However, the high recurrence rate after concurrent chemoradiotherapy makes the prognosis of patients with locally advanced cervical cancer not as expected^[3]. Recently, platinum-based neoadjuvant chemotherapy can effectively reduce the tumor volume, thereby providing the opportunity for surgery and improving the prognosis^[4] of locally advanced cervical cancer. Studies have^[5] confirmed that the chemotherapy sensitivity of patients with locally advanced cervical cancer is different due to individual heterogeneity. Recently, a number of in vitro studies have confirmed that excessive activation of autophagy is an important factor^[6] affecting the chemosensitivity of cervical cancer cells. mitogen-activated protein kinase kinase kinase-4 (MAP4K4) is an important factor involved in regulating the proliferation and invasion of cervical cancer cells. Recent in vitro studies have found that MAP4K4, Upregulation of MAP4K4 may activate autophagy to affect chemosensi^[7]tivity of cervical cancer patients. Tumor Hypoxia is a common feature of solid tumors. Hypoxia-inducible factors (HIF) are important factors involved in regulating the adaptation of solid tumors to hypoxia. HIF2 α has been confirmed to be up-regulated in cervical cancer patients, and is related^[8] to platinum-based chemotherapy drug resistance regulated by autophagy. However, the studies on MAP4K4 and HIF2 α are still at the in vitro cell level, and there is still a lack of high-level clinical cohort evidence, especially the neoadjuvant chemotherapy for locally advanced cervical cancer has not been reported. Based on this background, the aim of this study is to investigate the expression of MAP4K4 and HIF2 α in patients with locally advanced cervical cancer, and to clarify the effect of MAP4K4 and HIF2 α expression on autophagy activation and chemotherapy sensitivity, so as to provide new ideas for the subsequent early evaluation of chemotherapy efficacy in locally advanced cervical cancer.

1. Materials and Methods

1.1 General Information

A total of 230 patients with locally advanced cervical cancer admitted to our hospital from August 2022 to August 2025 were prospectively selected as the research objects. Inclusion criteria: ① Patients had not received any anti-tumor treatment before admission; ② Age of 40-60 years old; ③ received 3 cycles of neoadjuvant chemotherapy in our hospital after enrollment; ④ Cervical cancer confirmed by pathology; ⑤ patients voluntarily signed the informed consent; ⑥

International Federation of Gynecology and Obstetrics stage IB2-IIA2;^[9] ⑦ The pathological type was squamous cell carcinoma or adenocarcinoma. Exclusion criteria: ① Recurrent or metastatic cervical cancer; ② cognitive dysfunction, difficult to cooperate with the completion of the trial; ③ combined with malignant tumors in other parts of the body; ④ combined with immunodeficiency or immune-related diseases; ⑤ patients received neoadjuvant chemoradiotherapy before enrollment; ⑥ patients with hematological diseases; This study was approved by the ethics committee of our hospital. In the effective group of 161 patients, the average age was (51.85 ± 6.54) years old, the tumor size was $<5\text{cm}$ in 77 cases, $\geq 5\text{cm}$ in 84 cases, lymph node metastasis was 106 cases, no lymph node metastasis was 55 cases, histological type was adenocarcinoma in 95 cases, squamous cell carcinoma in 66 cases, clinical stage was Ib2 in 90 cases, iiA1-iiA2 in 71 cases, differentiation degree was: There were 65 cases of poor differentiation and 96 cases of moderate/high grade. In the ineffective group of 69 patients, the average age was (52.95 ± 6.78) years old, the tumor size was $<5\text{cm}$ in 33 cases, $\geq 5\text{cm}$ in 36 cases, lymph node metastasis in 106 cases, no lymph node metastasis in 55 cases, histological type: adenocarcinoma in 40 cases, squamous cell carcinoma in 29 cases, clinical stage: Ib2 in 39 cases, iiA1-iiA2 in 30 cases, differentiation degree: There were 28 cases of poor differentiation and 41 cases of moderate/high grade.

1.2 Methods

1.2.1 Baseline data collection of patients

The baseline information of all patients, including age and basic medical history, was collected by the responsible nurses of the department after enrollment, and routine enrollment education was carried out for patients. After pathological examination, the disease-related information of patients was retained, including tumor size, lymph node metastasis, clinical stage, pathological type, tissue differentiation degree, etc.

1.2.2 Neoadjuvant chemotherapy regimens

Before neoadjuvant chemotherapy with carboplatin and paclitaxel, all patients were treated with the same anti-emetic regimen. The specific chemotherapy regimen was d1, 175mg/m² paclitaxel, d2, carboplatin: area under the curve 4-5, intravenous infusion, repeated every 3 weeks, all patients were treated for 3 cycles.

1.2.3 Collection of peripheral blood samples

5ml peripheral venous blood samples were collected in the morning of the next day after enrollment (8 hours of fasting) and after 3 cycles of chemotherapy (8 hours of fasting). The blood samples were centrifuged at 1000r/min for 15min (10cm radius), the upper layer of serum was separated, and then centrifuged again at 1200r/min for 5min (10cm radius). After the centrifugation, 1.5mL of

serum was collected and stored in an enzyme-free centrifuge tube and placed in a refrigerator at -80°C until testing.

1.2.4 The expressions of MAP4K4, HIF2 α and autophagy-related factors LC-3II, LC-3I and Beclin-1 in peripheral blood were detected by qRT-PCR

Total RNA was extracted by Trizol method (Shanghai Shangbao Biotechnology Co., LTD.) and reverse transcription was performed by SYBRR Green fluorescent dye kit (Shanghai Win-win Biotechnology Co., LTD.) and ABI StepOne PCR instrument (Shanghai Lili Intelligent Technology Co., LTD.). The reverse transcription conditions were as follows: The reverse transcription operation was carried out at 98°C, 50°C and 37°C. After reverse transcription into cDNA, RT-PCR amplification was performed, and GAPDH was used as the internal control. The primer sequence was HIF2 α : Forward 5'-GAACATGG CCCCCGATGAAT-3', reverse-5'-CCCCTGAGCTCCTGGTAGAT-3'. MAP4K4-Forward-5'-CGGAATTCATGGCGAACGACTCCCCTGCAAAAAGTCTG-3'; Reverse - 5'-CCGCTCGAGCCAGCTCAGAAGAGAAGTCCTGCC - 3'. The reaction conditions were as follows: 65 ° C for 1min, 95 ° C for 15s, and 95 ° C for 10min. The last reference 2 was used to calculate the relative mRNA expression levels of MAP4K4, HIF2 α , LC-3II, LC-3I- $\Delta\Delta$ CT, and Beclin-1.

1.3 Efficacy evaluation criteria

According to the evaluation criteria^[10] of solid tumors, all patients included in this study were evaluated by B-ultrasound or MRI. The patients were divided into: Complete response (CR) : all target lesions disappeared; partial response (PR) : the sum of the long diameters of the target lesions reduced by 50% or more; stable disease (SD) : the target lesion increased by no more than 25% or decreased by less than 50%; progressive disease (PD) : target lesion enlargement by more than 25% or the appearance of new lesions. CR and PR were included in the effective group, and PD and SD were included in the ineffective group. A total of 161 patients achieved CR+PR in this study. A total of 69 patients had PD+SD.

1.4 Statistical Methods

SPSS20.0 software was used to analyze the data, and GraphPad Prism 8 was used for graphical drawing to represent the measurement data. Independent sample $\bar{x} \pm s$ t test was used for comparison between any two groups, and paired sample t test was used for comparison between the same group. The count data were expressed as percentage, and the comparison between any two groups was performed by chi-2square test. $P < 0.05$ was considered statistically significant.

2 Results

2.1 Relationship between the expression of MAP4K4 and HIF2 α in peripheral blood before chemotherapy and the pathological characteristics of cervical cancer patients

The expressions of MAP4K4 and HIF2 α in peripheral blood of patients with locally advanced cervical cancer were not significantly different among the subgroups of age, tumor size and histological type ($P > 0.05$), but were significantly different among the subgroups of differentiation degree, FIGO stage and lymph node metastasis ($P < 0.05$). For details, see **Table 1**.

Table 1. The relationship between MAP4K4 and HIF2 α expression in peripheral blood before chemotherapy and the pathological characteristics of patients with cervical cancer

Pathological features	MAP4K4 mRNA	t	P-value	HIF2 α mRNA	t	P-value
Age (years)						
< 50(n=125)	3.84 $\pm$ 0.31	1.26	0.21	3.87 $\pm$ 0.35	1.76	0.07
$\geq$ 50(n=105)	3.89 $\pm$ 0.29			3.80 $\pm$ 0.25		
Tumor size						
<5cm(n=110)	3.87 $\pm$ 0.21	1.61	0.10	3.85 $\pm$ 0.26	1.86	0.06
$\geq$ 5cm(n=120)	3.82 $\pm$ 0.26			3.78 $\pm$ 0.31		
Histological type						
Adenocarcinoma (n=135)	3.85 $\pm$ 0.21	1.59	0.11	3.81 $\pm$ 0.28	0.50	0.61
Squamous cell carcinoma (n=95)	3.80 $\pm$ 0.25			3.79 $\pm$ 0.31		
Degree of differentiation						
Poorly differentiated (n=93)	4.72 $\pm$ 0.35	26.51	0.00	4.67 $\pm$ 0.29	31.85	0.00
Moderately/well differentiated (n=137)	2.98 $\pm$ 0.64			2.87 $\pm$ 0.56		
FIGO stage						
Ib2 (n=129)	3.01 $\pm$ 0.31	41.02	0.00	3.11 $\pm$ 0.29	28.01	0.00
II a1~II a2(n=101)	4.61 $\pm$ 0.28			4.53 $\pm$ 0.44		
Lymph node metastasis						
None (n=152)	3.41 $\pm$ 0.38	17.86	0.00	3.35 $\pm$ 0.28	24.04	0.00
Yes (n=78)	4.26 $\pm$ 0.32			4.31 $\pm$ 0.29		

2.2 Expressions of MAP4K4 and HIF2 α in peripheral blood of the two groups before and after chemotherapy

Before chemotherapy, MAP4K4 mRNA and HIF2 α mRNA in peripheral blood of the two groups had no significant difference ($P > 0.05$). After chemotherapy, MAP4K4 mRNA and HIF2 α mRNA in the two groups were significantly decreased ($P < 0.05$), and MAP4K4 mRNA and HIF2 α mRNA in the effective group were significantly lower than those in the ineffective group ($P < 0.05$). Details are shown in **Table 2**.

Table 2. Expression of MAP4K4 and HIF2 α in peripheral blood before and after chemotherapy in the two groups of patients

Groups	MAP4K4 mRNA		HIF2 α mRNA	
	Before chemotherapy	After chemotherapy	Before chemotherapy	After chemotherapy
Effective group (n=161)	3.85 $\pm$ 0.31	1.75 $\pm$ 0.21	3.72 $\pm$ 0.22	1.63 $\pm$ 0.15
Ineffective group (n=69)	3.79 $\pm$ 0.35	2.98 $\pm$ 0.15	3.69 $\pm$ 0.18	2.78 $\pm$ 0.16
T-value	1.23	50.21	1.08	50.88
P-value	0.22	0.00	0.28	0.00

Note: a $P < 0.05$ compared with the same group before chemotherapy

2.3 Expressions of autophagy-related factors LC-3II, LC-3I and Beclin-1 in the two groups

Before chemotherapy, there were no significant differences in LC-3II, LC-3I and Beclin-1 between the two groups ($P > 0.05$). After chemotherapy, the levels of LC-3II, LC-3I and Beclin-1 in the two groups were increased, and the levels of LC-3II, LC-3I and Beclin-1 in the ineffective group were significantly higher than those in the effective group ($P < 0.05$). For details, see **Table 3**.

Table 3. Expressions of autophagy-related factors LC-3II, LC-3I and Beclin-1 in the two groups

Groups	n	LC-3II mRNA		LC-3I mRNA		Beclin-1 mRNA	
		Before chemotherapy	After chemotherapy	Before chemotherapy	After chemotherapy	Before chemotherapy	After chemotherapy
Effective group (n=161)		1.39±0.21	2.02±0.12a	1.12±0.31	1.87±0.18a	1.23±0.17	1.91±0.23a
Ineffective group (n=69)		1.43±0.15	2.98±0.12a	1.20±0.30	2.38±0.15a	1.21±0.21	2.68±0.22a
T-value		1.63	52.49	1.83	22.21	0.70	23.99
P-value		0.10	0.00	0.07	0.00	0.48	0.00

Note: a $P < 0.05$ compared with the same group before chemotherapy

2.4 The relationship between the expression of MAP4K4 and HIF2 α in peripheral blood and autophagy related factors LC-3II, LC-3I and Beclin-1 after chemotherapy

MAP4K4 and HIF2A were significantly positively correlated with LC-3II, LC-3I, and Beclin-1 ($P < 0.05$). See Table 4 for details.

Table 4. Relationship between the expression of MAP4K4 and HIF2 α in peripheral blood and autophagy-related factors LC-3II, LC-3I and Beclin-1 after chemotherapy

Groups	MAP4K4 mRNA		HIF2 α mRNA	
	r	p	r	p
LC-3II	0.52	<0.01	0.45	<0.01
LC-3I	0.49	<0.01	0.51	<0.01
Beclin-1	0.51	<0.01	0.49	<0.01

2.5 Univariate analysis of sensitivity to neoadjuvant chemotherapy in patients with locally advanced cervical cancer

The results of chemotherapy in the two groups were included in the logistics regression model as the dependent variable (effective =1, ineffective =0). The results showed that differentiation degree, FIGO stage, lymph node metastasis, LC-3II, LC-3I, Beclin-1, MAP4K4 and HIF2 α were risk factors ($P < 0.05$). Details are provided in Table 5.

Table 5. Univariate analysis of sensitivity to neoadjuvant chemotherapy in patients with locally advanced cervical cancer

Groups	Assignment	MMSE scores		
		OR	95%CI	P-value
Tumor size	<5cm=0, ≥5cm=1	1.031	0.897 ~ 2.131	0.261
Histological types	Adenocarcinoma =0, squamous cell carcinoma =1	1.123	0.789 ~ 1.987	0.535
Degree of differentiation	Low differentiation =1, medium/high differentiation =0	2.363	1.351 ~ 4.654	<0.001
FIGO staging	Ib2=0, iiA1-A2 =1	3.123	1.365 ~ 5.654	<0.001
Lymph node metastasis	No =0, yes =1	2.356	1.365 ~ 6.578	<0.001
LC-3II	<=2.51, ≥2.51=1	3.231	1.657 ~ 5.654	<0.001
LC-3I	<2.43=, ≥2.43=1	4.652	1.654 ~ 6.763	<0.001
Beclin-1	<2.39=, ≥2.39=1	3.654	1.785 ~ 5.987	<0.001
MAP4K4	<2.60=, ≥2.60=1	3.546	1.657 ~ 5.684	<0.001
HIF2 alpha.	<2.55=, ≥2.55=1	3.756	1.726 ~ 6.551	<0.001

Note: LC-3II, LC-3I, Beclin-1, MAP4K4 and HIF2α were all expressed after chemotherapy

2.6 Multivariate analysis of sensitivity to neoadjuvant chemotherapy in patients with locally advanced cervical cancer

The results of multivariate analysis showed that differentiation, FIGO stage, lymph node metastasis, LC-3II, LC-3I, Beclin-1, MAP4K4 and HIF2α were independent risk factors affecting the chemosensitivity of locally advanced cervical cancer patients ($P < 0.05$).

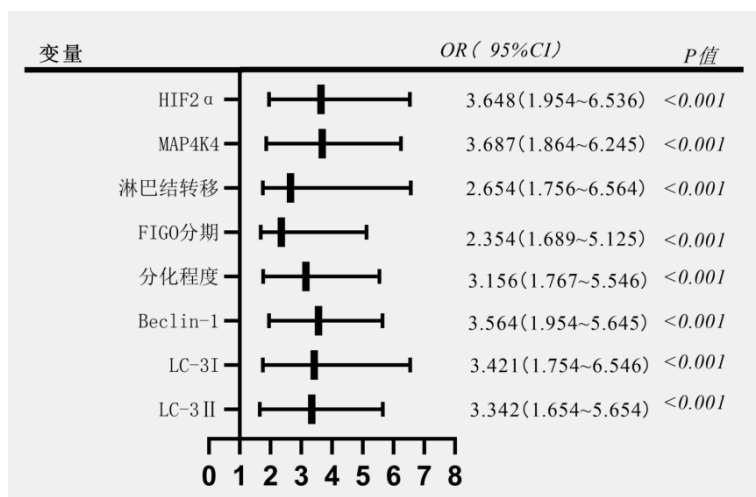


Fig.6. Multivariate analysis of neoadjuvant chemotherapy sensitivity in patients with locally advanced cervical cancer

3 Discussion

Sensitivity to neoadjuvant chemotherapy is an important factor affecting the prognosis of locally advanced cervical cancer. The results of this study showed that 30% (69/230) patients had poor sensitivity to neoadjuvant chemotherapy, which was similar^[11] to the results of Yang Yongbo et al. Therefore, it is of great significance to further find markers of early neoadjuvant chemotherapy sensitivity for locally advanced cervical cancer and guide the optimization of early treatment regimens.

MAP4K4 is located on chromosome 2q11.2 and contains 1200 amino acids with a molecular mass of 140 KDa. Initially, MAP4K4 was confirmed to be up-regulated in brain tissue and involved in the occurrence and development^[12] of atherosclerosis and cerebrovascular diseases. Recently, MAP4K4 has been found to play a particularly important role in the development of cancer and may be an important potential therapeutic^[13] target. MAP4K4 can inhibit the proliferation of tumor cells and block the progression of the disease by affecting the G0/G1 phase of tumor cells, which is an important idea for clinical intervention of the progressive development of breast cancer. Targeted regulation of MAP4K4 signaling pathway can effectively inhibit the proliferation and promote apoptosis^[14] of breast cancer cells. The alteration of immune microenvironment is an important pathological basis leading to the development of malignant tumors. The alteration of MAP4K4 expression can effectively regulate the immune microenvironment and affect the development^[15] of breast cancer. The important role of MAP4K4 in the progression of malignant tumors has also attracted the attention of cervical cancer researchers. Mei et^[16] al. found that up-regulation of MAP4K4 expression could effectively promote the proliferation and migration of cervical cancer cells by constructing an in vitro model of cervical cancer, suggesting that up-regulation of MAP4K4 expression may be related to the malignant development of cervical cancer. HIF2 α is an important member of the HIF family and plays an important role in regulating the adaptation of tumor cells and tissues to the hypoxic environment. The expression of HIF2 α in cervical cancer tissues is significantly higher than that in adjacent tissues, and the high expression of HIF2 α is closely related to lymph node metastasis and FIGO stage.^[17] Studies have confirmed that inhibition^[18] of HIF2 α expression can effectively inhibit G1 phase arrest and promote apoptosis of cervical cancer cells. The results of this study show that the expressions of MAP4K4 and HIF2 α are closely related to the degree of differentiation, FIGO stage and lymph node metastasis in patients with locally advanced cervical cancer, suggesting that the up-regulation of MAP4K4 and HIF2 α expression is closely related to the deterioration of the disease in patients with locally advanced cervical cancer.

The results of this study showed that MAP4K4 mRNA and HIF2 α mRNA expression levels in the effective group were significantly lower than those in the ineffective group after chemotherapy, suggesting that the up-regulation of

MAP4K4 and HIF2 α expression in patients with locally advanced cervical cancer is not only involved in the progressive development of the disease, but also related to the sensitivity to neoadjuvant chemotherapy during the peri-chemotherapy period. Autophagy is a kind of non-apoptotic cell death. It is a highly conserved process in eukaryotic cells, which has been proved to be a “double-edged sword” that plays a protective or detrimental role in ^[19]tumorigenesis. Studies have found that chemotherapy can activate autophagy in tumor ^[20] cells, and moderate autophagy activation can effectively promote the death of cancer cells and promote the efficacy of chemotherapy. However, evidence has shown that excessive activation of autophagy after chemotherapy in some patients leads to chemoresistance of tumor cells, which affects the efficacy of neoadjuvant chemotherapy. The results of this study showed that the expression of autophagy-related genes LC-3II, LC-3I and Beclin-1 in the effective group was significantly lower than that in the ineffective group, suggesting that the excessive activation of autophagy in patients with locally advanced cervical cancer is closely related to chemotherapy sensitivity. Jiang et al. showed in vitro that upregulation ^[21] of HIF2 α enhanced autophagy in cervical cancer cells under hypoxic conditions. In addition, the latest in vitro study by Jiang et al. confirmed that the up-^[8]regulation of HIF2 α expression was involved in the regulation of the sensitivity of cervical cancer cells to cisplatin. Huang et al. showed in vitro that upregulation of MAP4K4 could enhance autophagy in cervical cancer cells and reduce their sensitivity to platinum-based chemotherapy drugs. ^[22]The results of Pearson test showed that the expressions of MAP4K4 and HIF2 α were positively correlated with the levels of LC-3II, LC-3I and Beclin-1, which confirmed that the overexpression of MAP4K4 and HIF2 α was related to chemotherapy resistance in patients with locally advanced cervical cancer. Multivariate regression analysis showed that MAP4K4 and HIF2 α were independent risk factors for chemoresistance in patients with locally advanced cervical cancer. The results suggest that MAP4K4 and HIF2 α are up-regulated with the progression of cervical cancer, and the up-regulation of MAP4K4 and HIF2 α may promote the progressive development of cervical cancer by promoting tumor cell proliferation and inhibiting apoptosis. The overexpression of MAP4K4 and HIF2 α may promote the excessive activation of autophagy during chemotherapy, thereby reducing the sensitivity of cervical cancer cells to chemotherapy and ultimately affecting the efficacy of chemotherapy.

In summary, the present study has further demonstrated that MAP4K4 and HIF2 α are closely related to disease progression and resistance to platinum-based neoadjuvant chemotherapy in patients with locally advanced cervical cancer, which provides evidence for the clinical transformation of MAP4K4 and HIF2 α as reliable serum markers for early evaluation of chemotherapy efficacy in patients with locally advanced cervical cancer.

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