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# Expression of KAI1 and AGR2 in lung adenocarcinoma and their clinicopathological significance

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**Abstract**

**Objective:** Anticancer 1 (KAI1, tumor metastasis suppressor gene) and Anterior gradient-2 (AGR2, considered a valuable prognostic factor for some cancers) are associated with metastasis and prognosis of various types of human cancers. Nevertheless, the relationship between KAI1 and AGR2 in lung adenocarcinoma (LUAD) remains unclear. In this research, we analyzed the correlations between KAI1 and AGR2 in LUAD, and explored their correlations with clinicopathological parameters and overall survival time (OS) in patients with LUAD.

**Methods:** Immunohistochemical staining was used to detect KAI1 and AGR2 expression in 132 cases of LUAD samples. At the same time, all clinicopathological parameters and postoperative survival information were collected.

**Results:** AGR2 positive rate was significantly increased and KAI1 positive rate was significantly decreased in LUAD and control tissues. KAI1 positive rates were negatively correlated with tumor stage, LNM stage and TNM stage, and KAI1 subgroup positive expression of OS was significantly higher than negative KAI1 subgroup. The positive rate of AGR2 was positively correlated with tumor grade, LNM stage and TNM stage, and negatively correlated with patients OS. Active expression of AGR2 and KAI1, tumor stage, and LNM stage in multivariate analyses may be independent prognostic factors for OS in LUAD patients.

**Conclusion:** KAI1 and AGR2 may be potential biomarkers for prognosis and metastasis, and they are also promising therapeutic targets for LUAD patients.

**Abbreviations:** AGR2 = anterior gradient-2, EMT = epithelial-mesenchymal transition, KAI1 = anticancer 1, LNM = lymph node metastasis, LUAD = lung adenocarcinoma, OS = overall survival, TNM = tumor node metastasis.

**Keywords:** AGR2, KAI1, lung adenocarcinoma, prognosis

## 1. Introduction

LUAD is a subtype of non-small cell lung cancer, has surpassed lung squamous cell carcinoma in recent years to become the most common subtype of lung cancer accounts for about 40%.[1,2] Despite some progress in cancer treatment in recent decades, the accurate prognosis of LUAD is still not optimistic, and the 5-year overall survival rate is less than 15%.[3,4] Compared with other malignant tumors, the low survival rate means that the poor treatment effect. The main reason is that there are no obvious clinical symptoms at the early stage of LUAD, so its occurrence and development are difficult to predict. Most of the patients with early LUAD are found in physical examination, and most of the patients with LUAD presenting symptoms are already in the rapid progression of tumors development, with poor prognosis and high mortality.[5,6] Metastasis and recurrence of tumors are important reasons for poor prognosis.

KAI1 also known as CD82, is a tumor metastasis suppressor gene. It was discovered in recent years and initially thought to be a specific tumor metastasis suppressor gene expressed in prostatic cancer cells.[7] The KAI1 gene regulates cell membrane structure by interacting with integrins and other TM4SF proteins.[8] In addition, KAI1 can inhibit epithelial-Mesenchymal transition in tumor cells to play a specific biological role.[9] KAI1 also regulates biological behaviors such as the tumor cells migration, adhesion, differentiation, and invasion.[10] KAI1 regulates the Wnt/β-catenin signal pathway to enhance tumor cellular adhesion, stabilizes the E-cadherin/β-catenin pathway, also inhibits tumor cell from separating from the primary lesions,[11,12] but it inhibits the stimulating effect of β-catenin tyrosination on hepatocyte growth factor.[13] More and more studies have shown that KAI1 expression downregulation or loss promotes tumor metastasis and is closely related to poor prognosis in various types of human malignant cancers.[10]

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*The data that support the findings of this study are available from a third party, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are available from the authors upon reasonable request and with permission of the third party.*

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AGR2 is a human homologue capable of encoding secreted proteins, which was initially found in African xenopus.[14] AGR2 is also a member of the protein disulfide isomerase family, and has been found in endoplasmic reticulum.[15] As a member of the protein disulfide isomerase family, AGR2 is involved in protein folding and receptor protein maturation.[15,16] Studies have found that the endoplasmic reticulum is closely related to the occurrence and biological behavior of tumors.[17] AGR2 is also a pro-oncogene protein, expressed in various types of human malignant cancers, which can regulate p53-related signal transduction.[18]AGR2 also can induce EGFR ligand proteins to enhance cell survival and stimulate the growth of cancer cells.[19] AGR2 can also promote tumor cells proliferation, migration, metastasis and malignant transformation.[20,21] AGR2 is overexpressed in many human malignant cancers, such as lung, breast, prostatic, oral, and pancreatic cancers. In summary, it is also a useful biomarker for prognosis in clinical practice.[14]

In summary, continued studies of KAI1 and AGR2 suggest that these 2 biomarkers are involved in tumor prognosis and metastasis. However, the expression of KAI1 and AGR2 in LUAD, whether they are related, and their relationship with clinicopathological factors have not been widely reported. In this study, researchers detected the expression of KAI1 and AGR2 in LUAD, evaluated the hypothesis that these biomarkers are correlated, and analyzed their correlation with clinicopathological factors such as LUAD prognosis and metastasis.

## 2. Methods

### 2.1. Patients and clinical samples

Well-preserved tissue blocks of LUAD in the First Affiliated Hospital of Bengbu Medical College were collected. All the selected cases were confirmed by pathological diagnosis. A total of 132 cases were included in the study from January 2015 to December 2016. All the selected patients had well-preserved clinical history, pathological diagnosis and follow up data. This study was approved by the institutional ethical review board of First Affiliated Hospital of Bengbu Medical College. At the same time,132 adjacent non-tumor tissues of the same patient were selected as controls. Patients receiving preoperative anticancer therapy (chemotherapy, radiation, or any other anticancer therapy) were excluded. Postoperative follow-up of 138 selected patients was up to his/her date of death or December 2021 (mean survival: 38.8 months; Range: 5–76 months), data obtained to calculate OS. Clinical and pathological data were collected and tumor grade was assessed according to WHO standards, tumor LNM stage and TNM stage were assessed according to the 7th edition of American Joint Committee on Cancer. Specific features are shown in Table 1 below.

### 2.2. Immunohistochemistry

The dyeing operation was carried out by Using Elivision™Plus method, specifically according to the instructions of the kit purchased (Lab Vision). The steps are as follows: The sections are routinely deparaffinized to water. Buffer wash 3 min/2 times. In order to reduce the nonspecific background staining caused by endogenous peroxidase, incubate the sections in the Hydrogen Peroxide Block for 10 to 15 minutes. Then wash with buffer solution for 5 min/2 times. Add Ultra V Block dropwise and incubate at room temperature for 5 minutes to block nonspecific background staining. Wash with buffer solution 5 min/2 times. Drop the primary antibody working solution and incubate at 37℃ for 1 to 2 hours. Wash with buffer solution 5min/2 times. Add Primary Antibody Enhancer dropwise and incubate at room temperature for 20 minutes. Buffer wash 5 min/2 times. Add HRP Polymer (enzyme-labeled secondary antibody) dropwise and incubate at room temperature for 30 minutes. Buffer wash 5 min/2 times. Add 1 to 2 drops of DAB Plus Chromogen to 1 mL DAB Plus Substrate, mix them and add them to the slices, and incubate for 3 to 15 minutes. Then fully rinse with tap water, counter-stain, dehydrate, transparent, and mount the film.

### 2.3. Evaluation of staining

The immunohistochemical staining results were interpreted by 2 experienced pathologists using an independent double-blind method. KAI1 immunohistochemical positive cells were mainly located in the cytoplasm and membrane, while AGR2 positive cells were mainly located in the nucleus. The staining positive cell areas were selected, and at least 10 representative high magnification fields (HPF, magnification by 400) were observed under the microscope, the score was then based on staining intensity and percentage of positive cells. According to the staining intensity score: 0 = negative, 1 = weak, 2 = moderate, 3 = strong. Then the percentage of positive cells was calculated in each field of view: 0 was negative, 1 (10% or less), 2 (11%~50%), 3 (51%~75%), 4 (>75%). The final score was obtained by multiplying the 2 scores. The scores ≥ 3 is considered positive, otherwise it was deemed negative.

### 2.4. Statistical methods

Correlations between clinicopathological features and KAI1 and AGR2 expression were analyzed using the Chi-square test or the Fisher exact test. Spearman correlation coefficient method was used to analyze and compare the correlation between KAI1 and AGR2. The influence of KAI1 and AGR2 on postoperative OS was calculated and analyzed by univariate and multivariate COX regression methods. Survival analysis was performed using Kaplan–Meier and log-rank methods to assess the relationship

**Table 1**

**Patients characteristics.**

| Patients characteristics | Frequency (n) | Percentage (%) |
|---|---|---|
| Ages | | |
| <60 yr | 82 | 62.1 |
| ≥60 yr | 50 | 37.9 |
| Smoke | | |
| No | 53 | 40.2 |
| Yes | 79 | 59.8 |
| Gender | | |
| Male | 87 | 65.9 |
| Female | 45 | 34.1 |
| Size (cm) | | |
| <3.0 | 62 | 47.0 |
| ≥3.0, <7.0 | 66 | 50.0 |
| ≥7.0 | 4 | 3.0 |
| Tstage | | |
| T1 | 45 | 34.1 |
| T2 | 76 | 57.6 |
| T3 | 11 | 8.3 |
| Grade | | |
| Well | 50 | 37.9 |
| Moderate | 63 | 47.7 |
| Poor | 19 | 14.4 |
| LNM stage | | |
| N0 | 72 | 54.5 |
| N1 | 49 | 37.1 |
| N2 | 11 | 8.4 |
| TNM stage | | |
| I | 44 | 33.3 |
| II | 62 | 47.0 |
| IIIa | 26 | 19.7 |

LNM = lymph node metastasis, TNM = tumor node metastasis.

between KAI1 and AGR2 immunohistochemical staining results, clinicopathological factors and post-operative OS. Correlation between KAI1 and AGR2 staining results or clinicopathological characteristics was assessed using SPSS 26.0 (Chicago, IL). Statistically significant must comply with a value of $P < .05$.

## 3. Results

### 3.1. Correlations between KAI1, AGR2 and clinicopathological variables

Among the selected 132 cases of LUAD, 49 cases were positive for KAI1 immunohistochemical staining (49/132, 37.1%), among the corresponding non-tumor tissues, 114 cases were positive for KAI1 staining (114/132, 86.4%), $P < .05$ (Fig. 1A and B). 75 cases (75/132, 56.8%) were positive for AGR2 immunohistochemical staining. Among the corresponding non-tumor tissues, 26 cases (26/132, 19.7%) were positive for AGR2 staining, $P < .05$ (Fig. 2A and B). The positive expression rate of KAI1 and AGR2 in LUAD is positively correlated with tumor size, grade, LNM stage, TNM stage, but not correlated with the patients age, gender and smoking, $P > 0.05$ (Table 2).

### 3.2. Univariate and multivariate analysis

Using Kaplan–Meier method for univariate analysis, the results showed that the survival time of patients with positive KAI1 expression (54.0 ± 12.6 months) which was significantly higher than that of patients with negative expression of KAI1 (29.5 ± 8.9 months, Log-rank = 81.702, $P < .001$; Fig. 3A); The survival time of patients with positive AGR2 expression (28.1 ± 7.4 months) which was significantly lower than that of patients with negative expression of AGR2 (52.5 ± 12.9 months, Log-rank = 105.834, $P < .001$; Fig. 3B). The influence of clinicopathological factors on pOSoperative survival time of LUAD patients: For details See Table 3.

Multivariate analysis showed that KAI1 and AGR2 positive expression, as well as TNM and LNM stage, were independent prognostic indicators for LUAD (Table 4).

### 3.3. Correlation among KAI1 and AGR2 in LUAD

Spearman correlation coefficient analysis showed that in 132 LUAD tissues, the expression of KAI1 and AGR2 showed a negative correlation ($r = -0.755$, $P < .001$, Table 5).

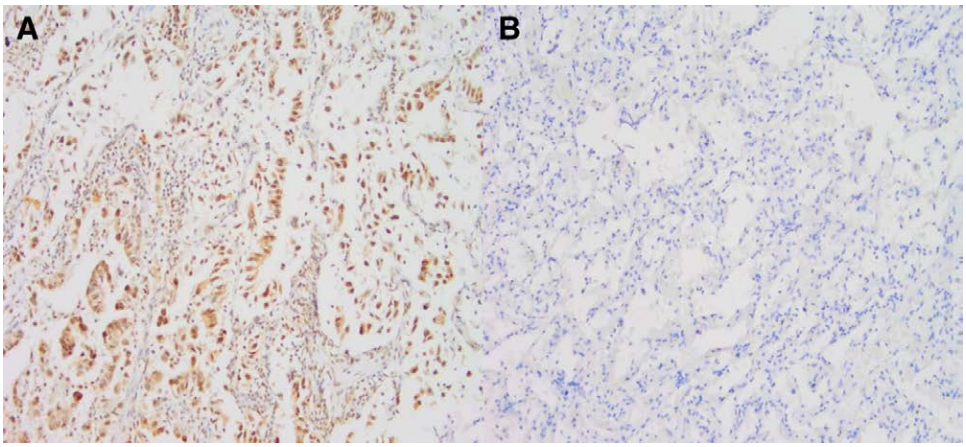


**Figure 1.** Immunostaining of KAI1 in LUAD or the control tissue. (A) The expression of KAI1 was negative in LUAD tissue (100 magnification). (B) The expression of KAI1 was positive in the control tissue (100 magnification). KAI1 = anticancer 1, LUAD = lung adenocarcinoma.

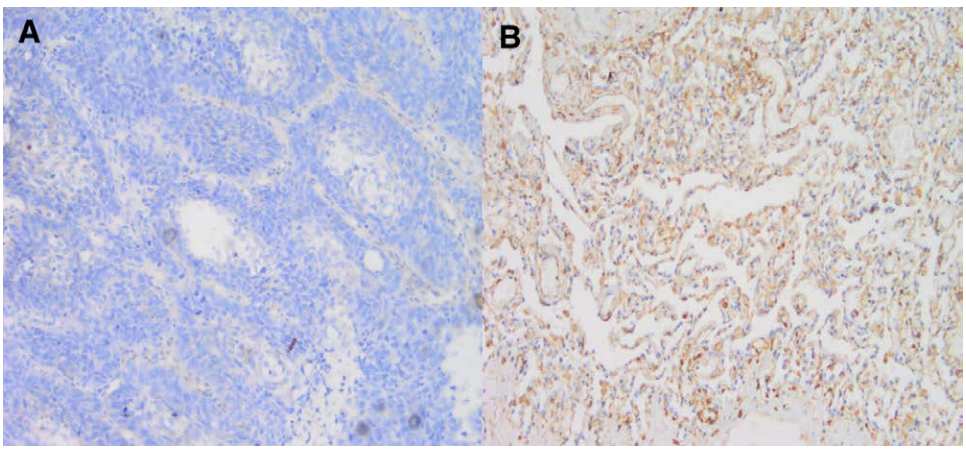


**Figure 2.** Immunostaining of AGR2 in LUAD or the control tissue. (A) The expression of AGR2 was positive in the LUAD tissue (100 magnification). (B) The expression of AGR2 was negative in the control tissue (100 magnification). AGR2 = anterior gradient-2, LUAD = lung adenocarcinoma.

**Table 2**

**The correlation between KAI1, AGR2 and clinicopathological characteristics in LUAD.**

| | KAI1 | | | AGR2 | | |
|---|---|---|---|---|---|---|
| **Variable** | **Negative** | **Positive** | ***P*** | **Negative** | **Positive** | ***P*** |
| Ages | | | .593 | | | .051 |
| <60 yr | 53 | 29 | | 30 | 52 | |
| ≥60 yr | 30 | 20 | | 27 | 23 | |
| Smoke | | | .728 | | | .751 |
| No | 34 | 19 | | 22 | 31 | |
| Yes | 49 | 30 | | 35 | 44 | |
| Gender | | | .789 | | | .833 |
| Male | 54 | 33 | | 37 | 50 | |
| Female | 29 | 16 | | 20 | 25 | |
| Size (cm) | | | <.001 | | | <.001 |
| <3.0 | 26 | 36 | | 37 | 25 | |
| ≥3.0, <7.0 | 53 | 13 | | 20 | 46 | |
| ≥7.0 | 4 | 0 | | 0 | 4 | |
| Grade | | | <.001 | | | <.001 |
| Well | 16 | 34 | | 34 | 16 | |
| Moderate | 49 | 14 | | 22 | 41 | |
| Poor | 18 | 1 | | 1 | 18 | |
| LNM stage | | | <.001 | | | <.001 |
| N0 | 27 | 45 | | 48 | 24 | |
| N1 | 46 | 3 | | 8 | 41 | |
| N2 | 10 | 1 | | 1 | 10 | |
| TNM stage | | | <.001 | | | <.001 |
| I | 8 | 36 | | 37 | 7 | |
| II | 50 | 12 | | 19 | 43 | |
| III | 25 | 1 | | 1 | 25 | |

AGR2 = anterior gradient-2, KAI1 = anticancer 1, LNM = lymph node metastasis, LUAD = lung adenocarcinoma, TNM = tumor node metastasis.

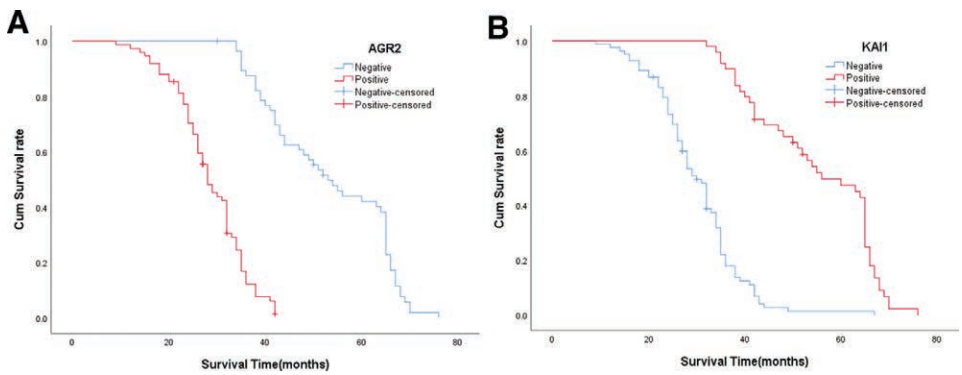


**Figure 3.** Kaplan–Meier analysis of the survival rate of patients with LUAD. (A) OS of all patients in relation to KAI1 expression (Log-rank = 81.702, $P < .001$); (B) OS of all patients in relation to AGR2 expression (Log-rank = 105.834, $P < .001$). AGR2 = anterior gradient-2, KAI1 = anticancer 1, LUAD = lung adenocarcinoma, OS = overall survival.

## 4. Discussion

LUAD is a highly heterogeneous malignant tumor, and its high heterogeneity may affect the effectiveness of biomarker evaluation.[5,6] For this reason, the role of biomarkers in tumor prognosis and metastasis should be thoroughly evaluated to ensure its effectiveness. Tumor recurrence and metastasis are the main reasons of tumor treatment failure. Therefore, it is necessary to constantly look for new and more effective biomarkers to evaluate and predict the prognosis of patients.

Inactivation of tumor metastasis suppressor genes plays an important role in the process of tumor cell metastasis.[9,10] As we all know, KAI1 is a tumor metastasis suppressor gene, which can inhibit the adhesion between cells and extracellular matrix, also can inhibit the metastasis of tumor cells by enhancing the adhesion between cells.[22] In this study, we found that the positive expression rate of KAI1 was significantly different between LUAD tissue and corresponding non-tumor control tissue. The positive expression rate was negatively correlated with tumor size, histological grade, TNM stage and LNM stage. In addition, statistical analysis showed that with the lower tumor differentiation, the later clinical stage, the lower expression level of KAI1. All these results indicated that down-regulation or deletion of KAI1 expression may promote the progression and metastasis of tumor cells, thus shortening the survival time of patients after operation and affecting the prognosis of patients. This is basically consistent with previous research results.[7–13,22]

Epithelial-mesenchymal transition (EMT) plays a key role in normal tissue development, inflammatory response and tumor cell metastasis. Some studies have shown that the overexpression of AGR2 is related to EMT process in tumor tissues.[23–25] In addition, the overexpression of AGR2 may also promote the growth and metastasis of tumor cells, and play an adverse role in clinical treatment.[23,26–29] In this study, we found that the expression of AGR2 in LUAD tissue was significantly higher than that in its corresponding non-tumor control tissue. In addition, we found that the overexpression of AGR2 was positively

**Table 3**

**Results of univariate analyses of overall survival (OS) time.**

| Variable | n | Mean OS(months) | Log-rank | *P* value |
|---|---|---|---|---|
| KAI1 | | | 81.702 | <.001 |
| Negative | 83 | 29.5 ± 8.9 | | |
| Positive | 49 | 54.0 ± 12.6 | | |
| AGR2 | | | 105.834 | <.001 |
| Negative | 57 | 52.5 ± 12.9 | | |
| Positive | 75 | 28.1 ± 7.4 | | |
| Ages | | | 0.196 | .683 |
| <60 yr | 82 | 44.1 ± 15.2 | | |
| ≥60 yr | 50 | 29.6 ± 12.3 | | |
| Smoke | | | 1.038 | .308 |
| No | 53 | 39.7 ± 17.8 | | |
| Yes | 79 | 38.0 ± 14.4 | | |
| Gender | | | 0.001 | .977 |
| Male | 87 | 39.0 ± 15.4 | | |
| Female | 45 | 37.9 ± 16.7 | | |
| Size (cm) | | | 58.613 | <.001 |
| <3.0 | 62 | 47.8 ± 16.2 | | |
| ≥3.0, <7.0 | 66 | 31.4 ± 9.4 | | |
| ≥7.0 | 4 | 15.8 ± 5.7 | | |
| Grade | | | | |
| Well | 50 | 49.5 ± 15.8 | 55.163 | <.001 |
| Moderate | 63 | 34.3 ± 11.3 | | |
| Poor | 19 | 24.5 ± 9.5 | | |
| LNM stage | | | 96.986 | <.001 |
| N0 | 72 | 47.8 ± 14.6 | | |
| N1 | 49 | 29.5 ± 7.6 | | |
| N2 | 11 | 19.5 ± 8.0 | | |
| TNM stage | | | 73.970 | <.001 |
| I | 44 | 53.3 ± 12.8 | | |
| II | 62 | 34.3 ± 11.5 | | |
| III | 26 | 24.1 ± 7.6 | | |

AGR2 = anterior gradient-2, KAI1 = anticancer 1, LNM = lymph node metastasis, TNM = tumor node metastasis.

**Table 4**

**Results of multivariate analyses of overall survival (OS) time.**

| Variable | B | SE | *P* | RR | 95.0% CI | |
|---|---|---|---|---|---|---|
| AGR2 | 2.148 | 0.363 | <.001 | 8.564 | 4.206 | 7.436 |
| KAI1 | –1.30 | 0.303 | <.001 | 0.878 | 0.466 | 1.655 |
| TNM | 0.51 | 0.235 | <.01 | 0.52 | 0.663 | 1.669 |
| LNM | 1.185 | 0.288 | <.001 | 3.270 | 1.861 | 5.748 |
| Grade | 0.427 | 0.184 | <.05 | 1.533 | 1.070 | 2.197 |

AGR2 = anterior gradient-2, KAI1 = anticancer 1, LNM = lymph node metastasis, TNM = tumor node metastasis.

**Table 5**

**Correlation among KAI1, AGR2 in LUAD.**

| | KAI1 | | | |
|---|---|---|---|---|
| Variable | Negative | Positive | r | *P* |
| AGR2 | | | –0.755 | <.001 |
| Negative | 12 | 45 | | |
| Positive | 71 | 4 | | |

AGR2 = anterior gradient-2, KAI1 = anticancer 1, LUAD = lung adenocarcinoma.

correlated with tumor size, TNM stage and LNM stage. Similar experimental results were found in other studies, which indicated that the overexpression of AGR2 was closely correlated with tumor progression and metastasis.[19–21,30]

In this study, multivariate COX regression methods showed that the positive expression of KAI1 and AGR2, TNM staging and LNM staging were independent prognostic factors for the survival of LUAD patients. Therefore, our results indicated that KAI1 and AGR2 should be regarded as useful biomarkers of LUAD, especially in predicting tumor metastasis and prognosis of patients.

As we all know, the metastasis of tumor cells should include a series of complicated processes, such as inactivation of tumor metastasis suppressor genes, activation of tumor metastasis factors and epithelial-mesenchymal transition. In this study, KAI1 expression was negatively correlated with AGR2 expression. Overexpression of AGR2 can promote proliferation, invasion, metastasis and EMT of tumor cells.[18] While the normal expression of KAI1 can inhibit EMT of tumor cells by strengthening β-catenin/ E-cad complex.[10,13] Therefore, the abnormal expression of KAI1 may lose the inhibition of tumor EMT, thus promoting the invasion and metastasis of tumor cells.

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