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Comparative study on the expression of Pax3, Rad51 and VEGF-C in esophageal gastric junction adenocarcinoma and distal gastric adenocarcinoma

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Abstract

The purpose of this study was to explore the differential expression of Pax3, Rad51 and VEGF-C in esophageal gastric junction adenocarcinoma and distal gastric adenocarcinoma and their relationship with cancer occurrence and development. 57 patients with gastric cancer were included and divided into esophageal gastric junction adenocarcinoma group (n=28) and distal gastric adenocarcinoma group (n=29). The positive expressions of Pax3, Rad51 and VEGF-C in the control group were lower than those in the esophageal gastric junction adenocarcinoma group and distal gastric adenocarcinoma group respectively (P<0.05). In esophageal gastric junction adenocarcinoma with low differentiation, positive expressions of Pax3, Rad51, and VEGF-C surpassed those in high/medium differentiation (P<0.05). Serosa-infiltrated cases exhibited higher Pax3 and Rad51 expressions compared to non-infiltrated cases (P<0.05). Rad51 and VEGF-C positivity were notably elevated in cases with lymph node metastasis compared to those without (P<0.05). Distal gastric adenocarcinoma displayed higher VEGF expression than middle/low differentiated adenocarcinomas. Rad51 expression was significantly higher in women than in men (P<0.05). The positive rates of Pax3, Rad51, and VEGF-C were markedly increased in esophageal gastric junction adenocarcinoma and distal gastric adenocarcinoma compared to normal gastric tissue, and these were associated with the degree of differentiation, depth of invasion, and lymph node metastasis in patients. Particularly, Rad51 exhibited a positive correlation with cancer cell differentiation, invasion depth, and lymph node metastasis in cancer tissue.

Keywords: esophageal gastric junction adenocarcinoma, Distal gastric adenocarcinoma, PAX3, RAD51, VEGF-C

1. Introduction

Gastric cancer stands as a formidable challenge within the landscape of malignant tumor diseases in our country, currently holding the unenviable position of being the most prevalent among such ailments. Its dominance is particularly noteworthy within the realm of digestive tract cancers, constituting a third of all cancer cases [1]. The gravity of this disease is further compounded by the emergence of a distinctive subtype known as adenocarcinoma of the esophagogastric junction (AEJ), which has garnered attention due to its heightened biological aggressiveness. Notably, AEJ exhibits a proclivity for lymph node metastasis and deeper invasion, elevating its clinical significance. Alarming trends indicate a gradual rise in the incidence of AEJ in recent years, prompting the need for comprehensive investigations into its underlying molecular mechanisms [1].

Studies have underscored the multifaceted nature of AEJ's etiology, emphasizing the interplay of various factors within the body [2]. Unraveling the intricate network of interactions that contribute to the genesis and progression of this specialized gastric cancer subtype is crucial for devising targeted therapeutic strategies. A pivotal aspect of this investigative endeavor involves scrutinizing specific molecular markers associated with cancer development and progression.

Among these markers, Vascular Endothelial Growth Factor C (VEGF-C) assumes a prominent role as a serum tumor marker. Recognized for its significance in cancer prediction, as well as the assessment of postoperative recurrence and metastasis, VEGF-C serves as an invaluable diagnostic indicator [1]. Its role in angiogenesis, facilitating the growth of new blood vessels within the tumor microenvironment, adds an additional layer of complexity to its involvement in cancer pathogenesis. Therefore, a nuanced understanding of VEGF-C expression is vital for unraveling the intricacies of AEJ and formulating effective prognostic and therapeutic interventions.

The DNA repair protein Rad51 emerges as another key player in the molecular landscape of AEJ. Its dynamic role encompasses a spectrum from underexpression, predisposing cells to embryogenic death, to moderate expression enabling repair of spontaneous DNA damage. Notably, overexpression of Rad51 is implicated in driving the occurrence and development of tumors, while concurrently diminishing the efficacy of chemoradiotherapy [3].

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This intricate duality positions Rad51 as a focal point in the delicate equilibrium between genomic stability and tumorigenesis, warranting a meticulous examination of its expression patterns in AEJ.

Adding to the complexity of molecular players is Pax3, an embryonic stemness gene intricately linked to glioma malignancy. High expression levels of Pax3 have been correlated with malignant biological behaviors, including increased glioma cell invasion, resistance to apoptosis, and enhanced proliferation. The investigation into Pax3 expression in AEJ provides a unique opportunity to delve into its potential implications for the aggressive nature of this gastric cancer subtype.

This study aimed to elucidate the impact of Pax3, Rad51, and VEGF-C expression on the development and progression of esophagogastric junction adenocarcinoma. By correlating their expression patterns in AEJ with those in distal gastric adenocarcinoma, we seek to establish a robust foundation for clinical approaches to the prevention and treatment of this disease. The comprehensive exploration of these molecular markers in the context of AEJ will contribute to a nuanced understanding of its pathogenesis, potentially paving the way for targeted therapeutic interventions and improved patient outcomes.

2. Materials and Methods

2.1. Patient data

Fifty-seven patients with gastric cancer diagnosed in our hospital from December 2020 to January 2022 were enrolled in this study. On the basis of the paraffin blocks of carcinomas of the patients, according to the location of the tumors, 28 patients were classified as the esophagogastric junction adenocarcinoma group, 29 patients as the distal gastric adenocarcinoma group, and 30 patients as the normal gastric mucosa tissues who underwent a health examination during the same period were also selected as controls. There were 22 males and 6 females in the esophagogastric junction adenocarcinoma group; Aged 53-75 years, with a mean age (66.25 ± 2.18) years. There were 24 males and 5 females in the distal gastric adenocarcinoma group; Age range 52-72 years, mean age (65.98 ± 2.03) years. The control group consisted of 23 males and 7 females; The age range was 54-73 years with a mean (SD) age of 66.17 ± 2.10 years. Compared with the general data of the three groups, $P > 0.05$, there was no statistical difference, and they were comparable. This study was approved by the ethics committee of our hospital, and all enrolled subjects were informed and consented for this study.

2.2. Immunohistochemistry (IHC)

Paraffin sections were deparaffinized to water using xylene for antigen heat retrieval, permeabilized with Triton solution (0.5%), incubated with H2O2 (3%), blocked again using goat serum, mounted with drops of primary antibody (diluted 1:1000 by TBS), incubated (4 ° C) overnight, incubated according to the method of the secondary antibody kit SP, DAB, developed, nuclei (hematoxylin counterstained), and differentiated (alcohol hydrochloride), diluted ammonia counter blue, dehydrated, Cover slips (neutral gums), and air dry 10 fields for taking photographs. Results were scored according to the intensity of staining, with 0 points for no positive coloration, 1 point for pale yellow, 2 points for yellow, and 3 points for tan. Final score = product of scoring results and positive cells (%). Staining results were quantified according to Image Pro Plus software, then relative expression was determined and lymphatic vessel density was calculated. The positive expression of Pax3, Rad51, and VEGF-C was observed and compared among the three groups, and their correlations with Pax3, Rad51, and VEGF-C expression were analyzed according to the following clinicopathological characteristics: patient age, gender, differentiation grade, tumor size, invasion depth, and lymph node metastasis.

2.3. Immunohistochemical positivity index analysis

Aipathwell digital pathology image analysis software was employed. The specific analysis process is as follows: (1) step: locate automatically and circle the area to be tested along the tissue to be tested, which can be positioned manually according to the specific requirements; (2) Color selection: automated positive judgment based on HSI, which can be corrected manually on a case by case basis; (3) Operations: on demand, the software automatically located the nucleus and extended the cytosolic range; The number of weakly, moderately, and strongly positive cells as well as the area were counted; Cumulative optical density IOD (integrated optical density); Different parameters such as tissue area. (4) Analysis: stepwise calculation of the area to be tested at high magnification. Upon completion, calculations on individual items are automated based on the original underlying data as well as algorithmic formulae to produce the analysis results, and a report is generated. H-SCORE=$\sum$(pi×i)=(percentage of weak intensity×1)+(percentage of moderate intensity×2)+(percentage of strong intensity×3) [4-7]

2.4. Procedure for fluorescence in situ hybridization (FISH) experiments on paraffin sections

Tissues were removed and washed and immediately placed in mounting solution (DEPC water formulated) for more than 12 h before fixation. After the completion of tissue fixation, the tissues were dehydrated through graded alcohols, immersed in wax, and embedded. Paraffin was sliced by a microtome, and slides were taken in a blender and baked in a 62°oven for 2 h. The sections were sequentially deparaffinized by placing them in xylene I 15 min-xylene II 15 min-absolute ethyl alcohol I 5 min-absolute ethyl alcohol II 5 min, air dried naturally, and DEPC water soaked. Depending on the length of tissue fixation time, sections were boiled for 10 min in repair solution and cooled down naturally. After gene stroke circle, according to different index properties of different tissues, proteinase K (20 ug/ml) was added dropwise to digestion at 37°C for 20 min. After washing with pure water, PBS was washed three times × 5 min. Prehybridization solution was added dropwise and incubated at 37°C for 1 h. Prehybridization solution was decanted and probe Pax/Rao51/VEGF containing hybridization solution was added dropwise at a concentration of 1um overnight in a humidified incubator with 42 degrees hybridization. The hybridization solution was washed away, and 2×SSC, 10 min wash at 37°C, 1×SSC, wash 2 at 37°C × 5 min, 0.5×SSC was washed for 10 min at room temperature. If there are more nonspecific hybrids, formamide washes can be increased. Sections were counterstained with DAPI dye dropwise for nuclei, incubated in the dark for 8 min, and mounted with anti-fluorescence quenching blocking agent dropwise

after rinsing. Sections were observed and images were acquired under a Nikon upright fluorescence microscope. (UV excitation 330-380 nm, emission 420 nm, blue; fam (488) green excitation 465-495 nm, emission 515-555 nm, green; Cy3 red excitation 510-560, emission 590 nm, red emission.) The nuclei stained by DAPI were blue under the excitation of ultraviolet, and the positive expression was the fluorescence of the corresponding fluorescein label. Fam (488) for green light and Cy3 for red light. MRNA in situ hybridization showed results theoretically cytoplasmic positive, with a few nuclear positive genera normal. The expression localization of different indicators was different between microRNAs and lncRNAs. There are strengths and weaknesses of fluorescence depending on the amount of expression. All reagents, instruments, etc. involved above require the use of an RNase-free environment after DEPC treatment for RNA in situ hybridization experiments.

2.5. Statistical analysis

The data of this study were analyzed by Statistic Package for Social Science (SPSS) 26.0 (IBM, Armonk, NY, USA), and the counting data were expressed by (n (%)) using the χ^2 test; Mg/dl) was used ($\bar{x} \pm s$) are indicated, compared by t-test; Spearman's method was used to analyze the correlation between Pax3, Rad51, and VEGF-C expression in cancer tissues. Differences were statistically significant when $P<0.05$.

3. Result

3.1. Morphological results of pathological sections of gastric cancer

After IHC detection of three indicators, the results showed that the staining of Pax3, Rad51 and VEGF-C proteins in the control group was significantly lighter than that in the other two groups, indicating that the positive expression of the three proteins was lower than that in the esophageal gastric junction adenocarcinoma group and the distal gastric adenocarcinoma group, respectively (Figure 1A). The positive index of immunohistochemistry was statistically analyzed and compared among the three groups. The results showed that the difference was statistically significant ($P < 0.05$) (Table 1).

At the same time, FISH was used to verify whether the DNA level of Pax3, Rad51 and VEGF-C was consistent with the results of immunohistochemistry. The results showed that the DNA expression of Pax3, Rad51 and VEGF-C in the control group was significantly lower than that in the other two groups, which was consistent with the results of immunohistochemistry. (Figure 1B)

3.2. Expression of Pax3, Rad51 and VEGF-C in esophageal gastric junction adenocarcinoma and distal gastric adenocarcinoma and their correlation with clinicopathological features

The positive expressions of Pax3, Rad51 and VEGF-C in the low differentiation degree of esophageal gastric junction adenocarcinoma were higher than those in the high/medium differentiation degree; The positive expression of Pax3 and Rad51 in infiltrated serosa was higher than that in uninjured serosa; The positive expressions of Rad51 and VEGF-C in patients with lymph node metastasis were significantly higher than those in patients without lymph node metastasis ($P < 0.05$). The positive expressions of Pax3 and VEGF-C in the high/medium differentiation degree of distal gastric adenocarcinoma were higher than those in the low differentiation degree; The positive expression of Rad51 in females was higher than that in males; The positive expressions of Pax3, Rad51 and VEGF-C in patients with lymph node metastasis were significantly higher than those in patients without lymph

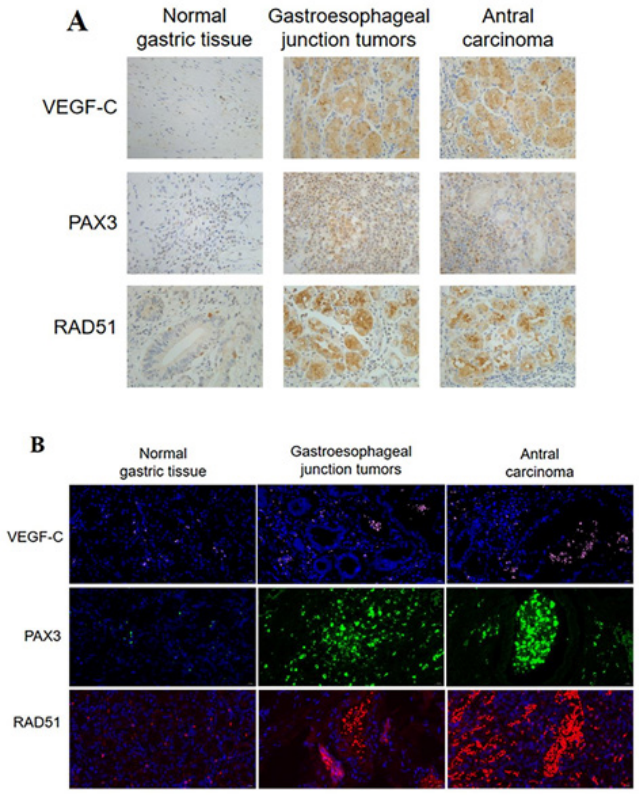

Fig. 1. IHC and FISH results of gastric cancer pathological sections. (A) IHC results for Pax3, Rad51, and VEGF-C proteins in gastric cancer pathological sections. (B) FISH results for Pax3, Rad51, and VEGF-C in gastric cancer pathological sections.

Table 1. Expression of PAX3, RAD51, VEGF-C in three groups (%).

Group	n	PAX3			RAD51			VEGF-C		
		positive	X^2	*P*	positive	X^2	*P*	positive	X^2	*P*
Normal gastric tissue	30	12 (40.00)			3 (10.00)			4 (13.33)		
Gastroesophageal junction tumors	28	27 (96.43)	20.936*	0.000*	20 (71.43)	22.838*	0.000*	21 (75.0)	22.457*	0.000*
Antral carcinoma	29	17 (96.55)	21.600#	0.000#	21 (72.41)	23.804#	0.000#	21 (72.41)	21.079#	0.000#

*Indicates the statistical value of the esophagogastric junction adenocarcinoma group compared with the control group# Statistical values are presented for the distal gastric adenocarcinoma group compared with the control group.

Table 2. Expression of Pax3, Rad51 and VEGF-C in esophageal gastric junction adenocarcinoma and their correlation with clinicopathological features.

Clinicopathological characteristics	n	PAX3			RAD51			VEGF-C		
		positive	X^2	*P*	positive	X^2	*P*	positive	X^2	*P*
Gender										
male	22	10 (45.45)	0.283	0.595	17 (77.27)	0.283	0.595	16 (72.73)	1.116	0.291
female	6	2 (33.33)			4 (66.67)			3 (50.00)		
Age										
<60	6	3 (50.00)	0.039	0.842	4 (66.67)	0.085	0.771	4 (66.67)	0.085	0.771
≥60	22	12 (54.55)			16 (72.73)			16 (72.72)		
Degree of differentiation										
High/Medium	24	6 (25.0)	3.930	0.047	4 (16.67)	6.222	0.013	5 (20.83)	4.929	0.026
Low	4	3 (75.00)			3 (75.00)			3 (75.00)		
Tumor size										
<5.0 cm	7	5 (71.43)	0.063	0.801	5 (71.43)	0.283	0.595	4 (57.14)	0.491	0.483
≥5.0 cm	21	16 (76.19)			17 (80.95)			15 (71.43)		
Invasion depth										
Non infiltrated serosa	23	6 (26.09)	5.200	0.023	7 (30.43)	4.230	0.040	13 (56.52)	0.949	0.330
Impregnated serofilm layer	5	4 (80.00)			4 (80.00)			4 (80.00)		
Lymph node metastasis										
No	20	12 (60.00)	0.560	0.454	9 (45.00)	4.215	0.040	6 (30.00)	4.725	0.030
Yes	8	6 (75.00)			7 (87.50)			6 (75.00)		

Table 3. Expression of Pax3, Rad51 and VEGF-C in distal gastric adenocarcinoma and their correlation with clinicopathological features.

Clinicopathological characteristics	n	PAX3			RAD51			VEGF-C		
		positive	X^2	*P*	positive	X^2	*P*	positive	X^2	*P*
Gender										
male	24	9 (37.50)	0.011	0.917	7 (29.17)	4.542	0.033	16 (66.67)	0.081	0.775
female	5	2 (40.00)			4 (80.00)			3 (60.00)		
Age										
<60	8	4 (50.00)	0.120	0.730	5 (62.50)	0.216	0.642	4 (50.00)	0.338	0.561
≥60	21	12 (57.14)			15 (71.43)			13 (61.90)		
Degree of differentiation										
High/Medium	28	23 (82.14)	3.970	0.046	25 (89.29)	0.120	0.730	24 (85.71)	4.971	0.026
Low	1	0 (0.00)			1 (100.00)			0 (0.00)		
Tumor size										
<5.0 cm	21	16 (76.19)	0.544	0.461	16 (76.19)	0.004	0.947	15 (71.43)	0.037	0.847
≥5.0 cm	8	5 (62.50)			6 (75.00)			6 (75.00)		
Invasion depth										
Non infiltrated serosa	8	4 (50.00)	0.684	0.408	5 (62.50)	0.216	0.642	5 (62.50) (62.5016)	0.544	0.461
Impregnated serofilm layer	21	14 (66.67)			15 (71.43)			16 (76.19)		
Lymph node metastasis										
No	24	7 (29.17)	4.542	0.033	6 (25.00)	5.541	0.019	7 (29.17)	4.542	0.033
Yes	5	4 (80.00)			4 (80.00)			4 (80.00)		

node metastasis (P<0.05). See Table 2 and Table 3. In the analysis of the expression of Pax3, Rad51 and VEGF-C by Spearman method, Rad51 was positively correlated with lymph node metastasis of esophageal gastric junction adenocarcinoma and distal gastric adenocarcinoma (r = 0.425, 0.392, P < 0.05).

4. Discussion

In recent years, it has been found that the composition ratio of gastric cancer in different locations changed significantly, and the incidence of AEJ increased significantly since there were no obvious symptoms in the early stage of AEJ and most patients were located in the middle and late stages at the time of presentation, resulting in a lower survival rate and poorer prognosis [8]. At this stage, many scholars have suggested that AEJ is a unique subtype in gastric cancer, and its immunohistochemical phenotype, pathological features, pathogenesis, and so on are quite

different from those of distal gastric cancer.

Clinical studies have shown that Pax3 can regulate cell proliferation through different pathways, contributing to cell self-renewal, influencing precursor cells to undergo directional metastasis and changing the differentiation direction of specific cells, and promoting tumor formation, tissue embryonic development, and other diseases [9]. Niedercan [10] scholars have pointed out that Pax3 is involved in the formation of glioma, and Pax3 expression has a certain inhibitory effect on glioma cells. The results of this study show that Pax3 expression in esophagogastric junction adenocarcinoma is significantly higher in terms of tumor differentiation, invasion, and the presence of lymph node metastasis. Both findings suggest that aberrant Pax3 expression may function as an oncogene in a variety of tumors.

VEGF belongs to an endothelial regulatory factor that induces proliferating endothelial cells and contributes to the generation of tumor internal and external vasculature, which is important for the division and proliferation process of lymphatic vessels and vascular endothelial cells in gastric cancer tissues [11]. VEGF-C is an important tumor lymphangiogenic factor, which is mainly produced in the autocrine or paracrine secretion of cancer cells and acts on peritumoral tissues, has a stimulatory induction effect on lymphatic endothelial cell migration, and proliferation, while forming lymphatic sinuses, and is closely related to tumor invasion and metastasis. The results of Tang Huan [12] scholars' research showed that the positive rate of VEGF-C in gastric cancer cancer tissues was significantly higher than that in adjacent normal tissues, and was related to tumor node metastasis, serosal invasion and so on. Consistent with the above findings, the positive rate of VEGF-C expression in esophagogastric junction adenocarcinoma was significantly higher in the infiltrated serosal layer and in the presence of lymph node metastasis. Both conclusions suggest that VEGF-C has the potential to be a major factor in predicting tumor lymphatic metastasis and prognosis.

Rad51 belongs to a family of DNA double-strand break repair proteins, mainly Acting in homologous recombination repair, which can play a certain role in protecting cells from DNA damage [13]. However, the excess of Rad51 will lead to homologous recombination and sister chromosome exchange, which will eventually cause genetic instability and divergence, cause immature differentiation and excessive proliferation of tumor cells, and develop tumors, leading to a poor prognosis. Werju [14] scholars showed that Rad51 expression was closely related to the degree of AEJ pathological differentiation, with or without lymph node metastasis, etc., the more severe the tumor malignancy in patients with higher Rad51 expression, the higher the expression of Rad51 in patients with lymph node metastasis. Our results also showed that Rad51 expression was significantly more frequently positive in AEJ with lymph node metastasis. As judged by the results of the two studies, Rad51 expression has the potential to contribute to lymph node metastasis at the AEJ and may be used as a reference standard for prognosis in patients with this disease. In addition, the results of this study also showed that the expression of Pax3, Rad51 and VEGF-C was analyzed by the Spearman method, and there was a positive correlation between Rad51 and cancer tissues with lymph node metastasis ($r = 0.425, 0.392, P < 0.05$). However, because limited by sample size, the result should be confirmed by further expansion tests. There are many genetic, biochemical, physiological, and epigenetic findings relevant to Gastric Cancer. [15-20].

In conclusion, Pax3, Rad51, VEGF-C expression is closely related to lymph node metastasis in esophagogastric junction adenocarcinoma, and especially, there is a positive correlation between Rad51 and cancer tissues, which may provide a new direction to test the occurrence and development of disease in patients.

Conflicts of interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Consent for publications

The author read and approved the final manuscript for publication.

Ethics approval and consent to participate

This study was approved by the ethics committee of Rushan people's Hospital.

Informed consent

Signed written informed consents were obtained from the patients and/or guardians.

Availability of data and material

The data that support the findings of this study are available from the corresponding author upon reasonable request

Authors' contributions

Qiang Pan and Chengyuan Yu have given substantial contributions to the conception or the design of the manuscript, Xiangyang Liu and Chen Xu to acquisition, analysis and interpretation of the data. All authors have participated in drafting the manuscript, Di Wu revised it critically. All authors read and approved the final version of the manuscript.

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Group name

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