

Research Progress on the Abnormal Expression of Galectin-3 and p16 in Cervical Cancer

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Abstract: Despite the increasing awareness of early diagnosis and treatment has brought about a downtrend in the morbidity and mortality of cervical cancer, recent years have still witnessed an obvious uptrend in the incidence rate among the young patients. Galectin-3 and p16, which play an important role in the incidence and development of cervical cancer and are closely related to its diagnosis and prognosis, are often used as important indicators of the clinical diagnosis of cervical cancer. This article reviews the protein structures of galectin-3 and p16 as well as their expression mechanism and abnormal expression regarding to cervical cancer.

Keywords: Cervical cancer, Galectin-3, p16

1. Introduction

In recent years, cervical cancer has become the second most common malignant tumors among women, after the breast cancer, with an uptrend among the younger populations^[1]. Based on the guidelines for the standard diagnosis and treatment of cervical cancer and precancerous lesions (for trial implementation) released by the National Health and Family Planning Commission of China, written in accordance with the rules of WHO Classification of Tumors (2003), the cervical cancer can be divided into squamous cell carcinoma of the cervix and cervical adenocarcinoma^[2]. At present, the diagnosis of cervical lesions is still based on pathological results. It is important to note that diagnostic errors caused by different pathologists and multipoint cervical biopsies are still inevitable. To improve the diagnostic accuracy of cervical cancer, it is necessary to know its etiology, thereby providing adequate theoretical basis of the diagnosis. Given the improvement in the field of molecular biology, galectin-3 and p16 become of particular interest in the research area of clinical pathology of cervical cancer. These two proteins, which play a strong part in the incidence and development of cervical cancer and are closely related to its diagnosis and prognosis, are commonly regarded as important indicators for the clinical pathological diagnosis of cervical cancer.

2. Research status of galectin-3

2.1. Structure and distribution of galectin-3

Galectin-3, a type of beta-galactoside-binding protein, is widely expressed in normal cells and tumor tissues. This protein can be found inside and outside of the cells, but it is

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expressed at a higher degree in the cells.

2.2. Role and potential application of galectin-3

Galectin-3 involves in multiple types of physiological and pathological processes, including cell growth, apoptosis, cell adhesion, migration, and infiltration of tumor cells. Overexpression of galectin-3 is observed in the growth process of many malignant tumors. During cancer progression, galectin-3 plays a regulatory role in the immunosuppression of tumor microenvironment and promotes tumor growth^[3]. Based on the study on the expression of galectin-1, galectin-3, and galectin-9 in squamous cell carcinoma of the cervix, CD163⁺ macrophages is the primary immune cell type of galectin-3, and galectin-3 is also expressed by a small number of T cells^[4]. With the adoption of polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP), Fu *et al.*^[5] investigated the relationship between the gene polymorphism of *galectin-3* and susceptibility as well as prognosis of cervical cancer. In addition, this study stated that Allele-C on the rs4652 locus of *galectin-3* might increase the risk for cervical cancer, thereby representing an indicator of bad prognosis. It was also found in the study of Fang *et al.*^[6] that Allele-C on the rs4652 locus and Allele-T on the rs11125 locus are potential risk factors for cervical cancer. Therefore, galectin-3 can be considered a reliable marker for tumor diagnosis and one of the therapeutic targets in the treatment of cancers.

2.3. Expression of galectin-3 in cervical cancer

2.3.1. Expression of galectin-3 in different cervical tissues

The current views with regard to the expression of galectin-3 in cervical cancers are opposing. With the adoption of quantitative reverse transcription polymerase chain reaction (RT-PCR), the expression of galectin-3 was found to be dramatically downregulated in the cells of cervical cancer compared to in normal tissues^[7]. In addition, galectin-3 was highly expressed in the squamous epithelial cells of cervix, but its expression decreased with the histopathological grade, as shown in this order: Low-grade squamous intraepithelial lesion >high-grade squamous intraepithelial lesion >invasive squamous cell carcinomas. In contrast, Yang *et al.*^[8] found that the protein concentration of galectin-3 was gradually increased with the clinical stages of cervical cancer.

A previous study indicated that the site of galectin-3 expression varied with the degrees of cervical lesions^[9]. In the tissues affected by chronic cervicitis, the expression of galectin-3 could be found in the cytoplasm, nucleus, and cell membrane, but the aggravation of the condition resulted in the lower expression rate in the nucleus but higher rate in the

cytoplasm^[9]. Meanwhile, it is possible that galectin-3 inhibits apoptosis and promotes the continuous progression of cervical lesions through its secretion from the nucleus to cytoplasm.

Based on a large volume of studies, the higher expression of galectin-3 is an indication of the higher degree of malignancy of cervical cancer. However, the studies on the dysregulated expression of galectin-3 in cervical cancer in the Chinese populations are still in their infancy. Thus, it is of paramount significance to unravel the role of dysregulated expression of galectin-3 in the development and progression of cervical cancer.

2.3.2. Factors affecting expression of galectin-3 in cervical cancer

2.3.2.1. Tumor size

Zhao *et al.*^[10] found that the high expression of galectin-3 did not correlate with the tumor size of patients with squamous cell carcinoma of the cervix. However, some studies showed that there were significantly statistical differences of positive expression rates between the cervical tumors of size ≤ 2 cm and those of size > 2 cm, supporting the perspective that an increased expression of galectin-3 is related to bigger size of tumor^[11].

2.3.2.2. Histopathological type of tumor

Some experiments showed that no significant differences of galectin-3 expression were found in different cervical tissues, but the results indicated that the protein expression of galectin-3 in non-squamous cell carcinoma of the cervix was higher than in the cervical neoplasia tissues and normal cervical tissues^[12]. However, Chen *et al.*^[13] reported that the expression of galectin-3 was irrelevant to the histopathological type of cervical cancer.

2.3.2.3. Infiltration degree of tumor

Li *et al.*^[14] reported that the galectin-3 expression was related to deep muscular infiltration of cervical cancer. However, some experiments indicated that there were no association between the positive expression rates and infiltration depth of cervical cancer between $\leq 1/2$ and $> 1/2$ ^[15].

2.3.2.4. Differentiation degree and histopathological grade of tumor

With the use of immunohistochemistry, Li *et al.*^[16] found that the expression of galectin-3 was irrelevant to the differentiation degree of cervical cancer. However, Tang *et al.*^[17] demonstrated that the positive expression of galectin-3 in squamous cell carcinoma of the cervix was obviously increased before lymphatic metastasis occurred. Wu *et al.*^[18] indicated in their study that a higher expression rate of galectin-3 was associated to the higher histological

grade of cervical cancer.

2.3.2.5. Lymphatic metastasis

There are divergences when it comes to the association between galectin-3 expression and lymphatic metastasis status^[19]. On the other hand, Xu *et al.*^[20] found that the expression of galectin-3 in cervical cancer tissues was irrelevant to the fact that whether the patient had lymphatic metastasis or not. Some research results indicated that galectin-3 expression is associated with lymphatic metastasis. For instance, as reported by Tang *et al.* that positive expression rate of galectin-3 in squamous cell carcinoma of the cervix increased before lymphatic metastasis occurred^[17], galectin-3 might be related to the occurrence of lymphatic metastasis in cervical cancer.

2.3.2.6. Clinical stages of tumor

In some studies, no remarkable statistical difference was found between the expression of galectin-3 and patients' FIGO grades^[21]. However, a study found that the expression of galectin-3 in endometrial adenocarcinoma was lower in the early stage than in the late stage, and the high expression of galectin-3 was associated with poor prognosis of cervical cancer, indicating that the abnormal expression of galectin-3 is relevant to the clinical stage of the tumor^[22]. Meanwhile, the expression of galectin-3 in endometrial adenocarcinoma was unrelated to the fact that whether the patient was in menopause or not, but the expression of galectin-3 in early-stage endometrial adenocarcinoma was remarkably lower than in end-stage cancer^[22].

In general, most studies support that the patient's age, ethnicity, and menopause status are irrelevant to the high expression of galectin-3 in cervical cancer. However, a large number of experiments are needed to unravel other factors that could affect the expression of galectin-3.

2.3.3. Clinical significance of galectin-3 expression in cervical cancer

Dietlmeier *et al.*^[23] verified that the high expression of prostaglandin EP2 receptor and galectin-3 could be considered the prognostic factor affecting the overall survival of patients with cervical cancer. Furthermore, the same study showed that the increased expression of galectin-3 in patients with invasive cervical cancer might indicate an increased risk for pelvic lymph node metastasis. Simultaneously, the research manifested that the increased protein expression might result in the tolerance of tumors to radiotherapy.

Li *et al.*^[24] thought that galectin-3 was closely related to the pathogenesis, development and especially infiltration of cervical cancer. By improving the homogeneous aggregation ability of cervical cancer cells, the invasion

and metastatic abilities of galectin-3 were enhanced to further promote the expansion of tumor lesions. In addition, galectin-3 was in positive correlation with the expression of vascular endothelial growth factor in the serum, indicating that galectin-3 promotes the progression of cervical cancer by playing its role in tumor-associated angiogenesis. Liu *et al.*^[25] also showed that the expression of galectin-3 was associated with the mortality of cervical cancer.

Based on the literature, galectin-3 expression could be regarded as a significant indicator cervical cancer diagnosis and as prognostic factor. Nevertheless, the mechanism behind the involvement of galectin-3 in the pathogenesis and development of tumors remains unclear. Therefore, it is of great importance to undertake more studies to unravel the role and future application of galectin-3 in the clinical aspects of cervical cancer.

3. Research status of p16

3.1. Role of p16

p16^{INK4a}, a type of profilin, is the product of the tumor suppressor gene *p16* made up of 148 amino acids. p16 engages in the regulation of cell cycle, proliferation, and division of cells. A decrease of p16 in cells can result in canceration^[26].

3.2. Expression of p16 in cervical cancer

Fu *et al.*^[27] indicated that after continuous infection with human papillomavirus (HPV) in the cervix, the expression of became elevated and the cells entered a state of unlimited proliferation. Some studies showed that p16 expresses in various grades of cervical lesions and cervical cancer^[28].

3.2.1. Expression of p16 in squamous cell carcinoma of the cervix

Zhai *et al.*^[29] indicated that the positive expression rates of p16 in different grades of squamous cell carcinoma of the cervix were different and found that p16 expression increased with the grade. The findings also indicated that the degree of expression of p16 was associated with the severity of squamous cell carcinoma of the cervix. In addition, the patient with higher degree of expression of p16 was more likely to have metastasis. The above-mentioned observation was supported by other study^[30]. In an experiment that determined the expression of p16^{INK4a} in the tumor budding area and central area of squamous cell carcinoma of the cervix, 32.5% of the specimens manifested with high expression of p16 and 67.5% with low expression in the central area of tumor, while 67.5% of specimens exhibited high expression of p16 but 32.5% presented with low expression in the tumor budding area^[31]. The findings also indicated that the increased expression of P16 was associated to the increased invasiveness of

cervical cancer.

According to the studies concerning the expression of p16 in squamous cell carcinoma of the cervix, p16 can be considered as one of the major predictive markers of cervical squamous epithelial lesions as well as biological behaviors and prognosis of squamous cell carcinoma of the cervix since the susceptibility to developing cervical squamous cell cancer is greater when the degree of expression of P16 is higher. In addition, it is also important to note that the increase in the invasiveness of cervical cancer and risk of metastasis is accompanied by the elevation of p16 expression.

3.2.2 Expression of p16 in cervical adenocarcinoma

Eleutério *et al.*^[32] reported that 66% of the patients with invasive cervical adenocarcinoma had positive expression of p16, suggesting the close association of p16 with the pathogenesis and development of adenocarcinoma. In an experiment that studied the expressions of P16 in endometrioid adenocarcinoma and cervical adenocarcinoma using immunohistochemistry, Li *et al.*^[33] suggested that p16 was a significant indicator for the clinical diagnosis of the two types of adenocarcinoma: endometrioid adenocarcinoma and cervical adenocarcinoma. In addition, using immunohistochemistry PV-9000 two-step method to determine the expression of p16 in patients with cervical adenocarcinoma (research group) and 60 cases of women with normal cervix (control group), Wang *et al.*^[34] found that the positive expression rate of p16 in normal cervix was lower than in patients with primary cervical adenocarcinoma. The finding suggests that p16 plays an important role in distinguishing between malignant and benign cervical adenocarcinoma. In addition, the results showed that, among the specimens of cervical adenocarcinoma, the positive expression rate of p16 in 46 HPV-positive cases was 95.7%, significantly illustrating the correlation between HPV infection and p16 expression. Some studies^[35] indicated that many HPV genotypes were relevant to cervical cancer. Almost all tumors associated with HPV infections have a strong expression of P16. In addition, among HPV-positive patients, negative expression of p16 is a prognostic marker for poor survival.

The high expression of p16 in cervical adenocarcinoma is associated with HPV infection. p16 is expressed in different types of cervical adenocarcinoma. It plays a significant role in the diagnosis and treatment of cervical adenocarcinoma and can be used to identify the tumor differentiation, grades and metastasis of patients with cervical adenocarcinoma.

4. Association between galectin-3 and p16

in cervical cancer

Studies on the association between galectin-3 and p16 in cervical cancer are scanty. Nevertheless, in a study that analyzed the expression levels of E6, p53, p16, MDM2, and galectin-3 in cervical cancer specimens using immunohistochemistry and semi-quantitative scoring, Stiasny *et al.*^[36] found that the expression levels of E6, P53, and P16 in squamous epithelial tissues had remarkable differences, and the expression levels of MDM2 and galectin-3 in cervical cancer were in positive correlation. In addition, in p16-negative cases, the abnormal expression of galectin-3 was associated with the poor prognosis of cervical cancer. However, the correlation of abnormal expression of P16 and galectin-3 in cervical cancer deserves further exploration.

5. Conclusion

Galectin-3 is a potential candidate of diagnostic and prognostic marker of cervical cancer. In addition, the development of galectin-3 inhibitors is currently underway, holding out hope that these inhibitors might have anti-tumor effect. Similarly, p16 is becoming one of the significant indicators for the diagnosis and prognosis of cervical cancer. To confirm their roles in diagnosis and prognosis of cervical cancers, large-scale studies are necessary to validate their utility and efficacy.

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Conflict of interest

The authors declared that they have no conflict of interest.

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