

Research Article

Effects of MMP1, EFNA1, ANLN and ZWINT Expressions on the Progressivity and Prognosis of Cervical Squamous Cell Carcinoma

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ABSTRACT

We conducted a review of MMP1, EFNA1, ANLN, and ZWINT expression and their relationship to the severity and prognosis of cervical carcinoma. Cervical cancer is the most common type of malignancy in gynecology, and its most common type is squamous cell. High incidence followed by high mortality rate and still occurring now despite numerous screening efforts. MMP1, EFNA1, ANLN, and ZWINT expressions were significantly found increase even reach the overexpression state along with the increasing cervical carcinoma severity. Its expression is higher in cervical carcinomas with metastases compared to without metastases and normal cervical tissue. Even in pre-cancer expression has been found increased. High expression is inversely proportional to the possibility of survival rate. The higher the expression, the worse the prognosis will be, and the shorter survival rate.

Keywords: MMP1, EFNA1, ANLN, ZWINT, cervical squamous cell carcinoma**INTRODUCTION**

Cervical cancer is a type of malignancy that is most often found in the gynecology field. More than 500,000 cases of incidents occur each year, with 3/5 of all cases ends in death.¹ Although various screening methods have been developed, such as Papanicolaou or Pap Smear tests, the mortality rate is still high.² And 90% of all deaths from cervical cancer in the world occur in developing countries.³ Approximately 80-90% of cervical cancers are squamous cell carcinoma types.⁴ Human papilloma virus (HPV) infection is one of the factors that trigger tumorigenesis in this disease, especially HPV-16.^{5,6} Cervical cancer is the result of a long disease course, starting with a cell change called cervical intra-cell neoplasia (CIN) that progresses from mild, moderate to severe which ends in cervical cancer. In the pathological process, tumor cell

infiltration occurs into lymphocyte cells or so-called tumor-infiltrating

lymphocytes (TIL),⁷ as a result, immune cells will experience damage and change in activity. Since this pathogenesis is known, many studies have been conducted to observe the prognosis of cancer based on the level of gene expression in tumor tissue.^{8,9,10}

Matrix metalloproteinase 1 or MMP1 is a protease that plays a role in the occurrence of proteolysis and extracellular matrix.¹¹ Research has found that its expression is increased in many types of cancer, such as prostate cancer, and it is an aspect that influences the prognosis of the cancer. MMP1 is also considered to be a trigger factor for glioma cell invasion in brain cancer.¹²

Ephrin A1 or EFNA1 is a protein that encodes ephrin. Ephrin itself involved in signalling in various conditions, for example in cell

proliferation. In addition, EFNA1 plays a role in the progression of malignancy, for example its expression is increases in melanoma.^{13,14}

At present, the standard treatment for cervical cancer patients is radiotherapy. Previously, studies in lung cancer patients showed that ANLN expression was reduced after receiving radiation therapy,¹⁵ so the expression of ANLN was also considered to be a potential aspect of evaluation for the evaluation of radiation therapy in cervical cancer.

Whereas ZW10 interacting kinetochore or ZWINT is a gene coding protein that is involved in kinetochore function. Its role is very important in the process of meiosis to separate homologous chromosome. ZWINT hyperexpression is found in malignant conditions, for example studies have identified it in prostate cancer due to castration resistance.¹⁶

DISCUSSION

Research by Zhao et al observed the expression of 4 genes using several cervical cancer samples and compared them with the expression in normal cervical tissue samples, namely the MMP1, EFNA 1, ANLN and ZWINT genes. They also calculated using the Cox's proportional hazards model of each genes to determine survival rate predictions related to gene expression levels.¹⁷

The results showed the MMP1, EFNA 1, and ANLN genes had a hazard ratio >1 which meant that the expression of these three genes was a risk factor, while the hazard ratio value of ZWINT <1 indicated it was a protective factor. In addition, this study also significantly demonstrated an increase in mRNA expression from all four gene in cervical cancer samples compared to normal cervical tissue samples.¹⁷

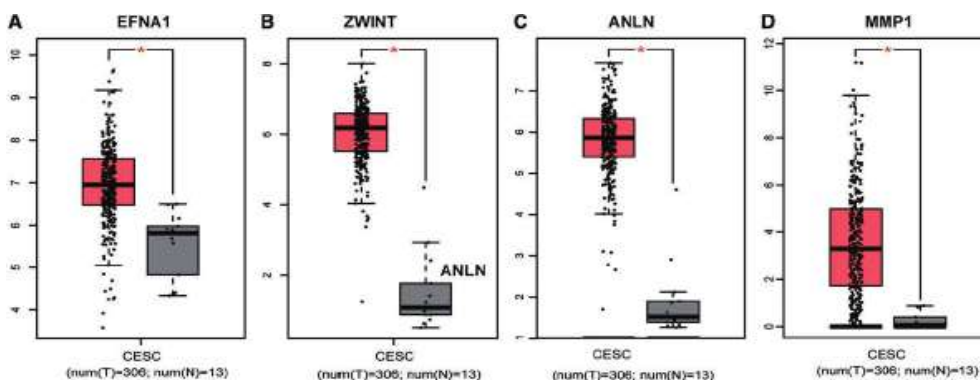


Fig.1: Comparison of EFNA 1, ZWINT, ANLN and MMP1 gene expression levels in cervical cancer samples compared with normal cervical tissue samples in the GEPIA17 database¹⁷

MMP1 expressions aside from being prognostic also help in the selection of therapeutic methods. MMP1 plays a role in the formation of cytokine signals for immune response, but this study shows that MMP1 expression is only associated with the incidence of tumor cell infiltration into

macrophages only, not on memory T cells, so if MMP1 gene expression is not high enough then the immunotherapy method is not appropriate.¹⁷ In general, the group of patients with higher expression of the four genes has a shorter survival rate than the group of patients with lower gene expression.¹⁷

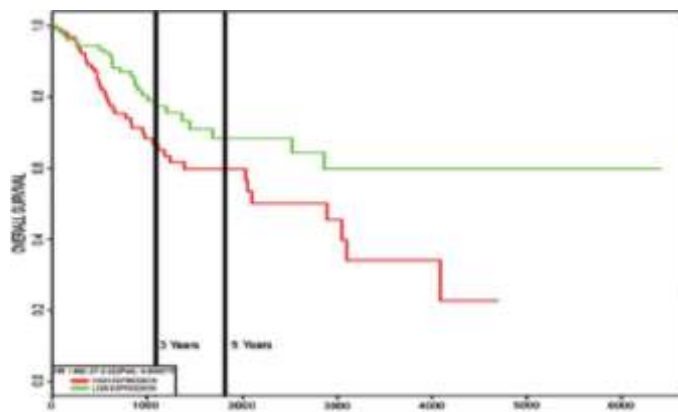


Fig.2: Higher gene expression causes shorter estimates of survival rate¹⁷

MMP1 is the target of has-miR-508, has-miR-509-2 and has-miR-526b. Many previous studies have recommended that these three messenger RNA or miRNA be used as aspects in the diagnosis and prognostic assessment of cervical cancer. miRNA is involved in the regulation of human genes and it is active in cell cycle regulation, apoptosis and cell proliferation. 18,19,²⁰

Research by Chen et al shows that the high MMP1 in cervical cancer can be inhibited by has-miR-508 and has-miR-509-2, especially in cervical cancer without metastasis to lymph nodes. Whereas in cervical cancer that has been accompanied with metastasis to lymph nodes, MMP1 expression is increasing, while the expression of has-miR-508 and has-miR-509-2 is actually lower. And the prognosis worsens with the weakening of miRNA and the strengthening of MMP1 expression.²¹

Tian et al conducted a study to identify genes that persistently and consistently had significant levels of expression to be used as biomarkers of cervical cancer, both for prognostic and identification of metastasis. Using 132 cervical cancer RNA data without metastasis to lymph nodes and 60 with metastases to lymph nodes, the results showed 11 genes found with high levels, but only MMP1

persistently showed hyperexpression. The expression level of MMP1 in cervical cancer with metastasis is higher than without metastasis. From these results can be seen that MMP1 expression is positively correlated with the severity of cancer that is occurring, and negatively correlated with survival rate. At MMP1 with lower expression, survival reaches 0.8% for more than 6000 days ahead. However, on MMP1 expression the high level of survival is only around 0.2% for the next 3,000 days.²²

Another study by Zhao et al was conducted to find prognostic aspects for cervical cancer. They identified 169 genes that had increased expression in cervical cancer tissue compared to normal tissue samples. And from all of these genes, obtained 5 genes that have significant p values with multivariable cox proportional hazards analysis test. Two of them are MMP1 and EFNA1. They then conducted The Kaplan-Meier analysis to find out the status of survival rate over the next few years. In general, survival values were shorter in groups with high gene expression. The MMP1 and EFNA1 gene hazard ratio are 1,123 and 1,1479 respectively.²³

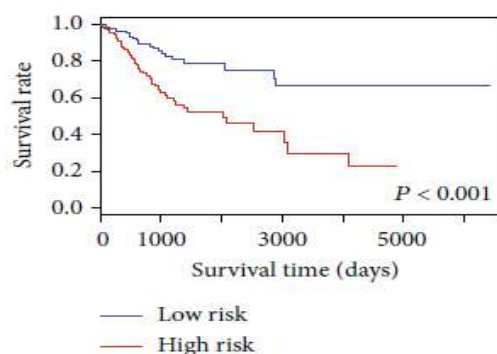


Fig.3: Survival analysis using The Kaplan-Meier²³

ANLN is a protein coding gene whose expression is normally found high in several organs, such as the brain. However, excessive expression indicates a condition of malignancy.^{24,25,26} Research by Xia et al specifically observed the expression of the ANLN gene in cervical cancer compared with samples of normal cervical tissue, as well as its

relationship to survival period. The results show a similar conclusion, that the ANLN expression is significantly higher in cervical cancer than in normal cervical tissue. And in general, high ANLN expression significantly shortens in survival rate, which means that the prognosis will get worse with increasing ANLN gene expression.²⁷

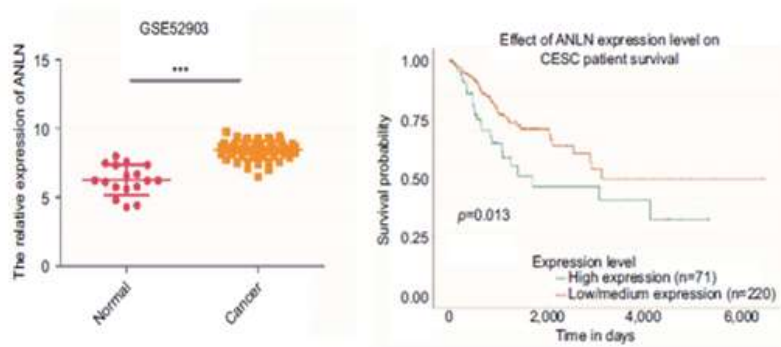


Fig. 4: ANLN gene expression is higher in cervical cancer than normal cervical cells and high gene expression results in shorter survival rate²⁷

Wei et al conducted a study with 75 cervical cancer tissue samples and 35 normal tissue samples. The results showed 73 genes were consistently identified, of which 65 genes experienced increased expression, and 3 of them produced the worst prognosis. One of the three genes is ANLN. The relative risk calculated by statistical survival analysis or hazard ratio techniques shows that

people with high ANLN expression have a 1.87 higher risk than groups with lower ANLN expression.²⁸ Tang and colleagues' results showed that there were 20 of the most significant genes that had increased expression and played a major role in the progression of cervical cancer, one of them was ZWINT, which was ranked 18.²⁹

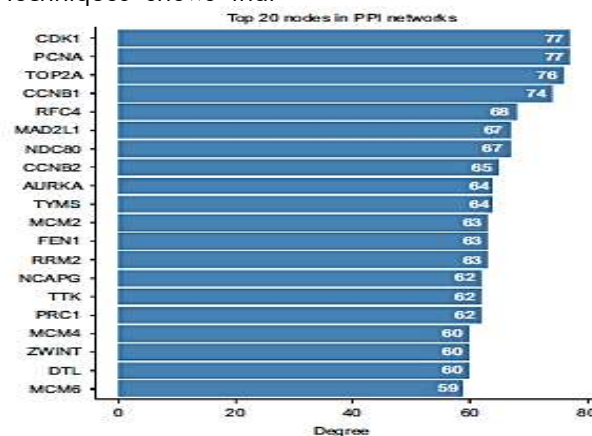


Fig.5: ZWINT is among the 20 most significant genes that has increased expression (60 degrees).²⁹

Of the many genes that have been identified from the cancer cells, Suman et al conducted a study to look at the expression of genes that consistently

expressed in the pre-cancer phase (CIN 2 and CIN 3) and cancer phase. The results found five genes that continue to appear in all phases or stages, one of them is ZWINT.³⁰

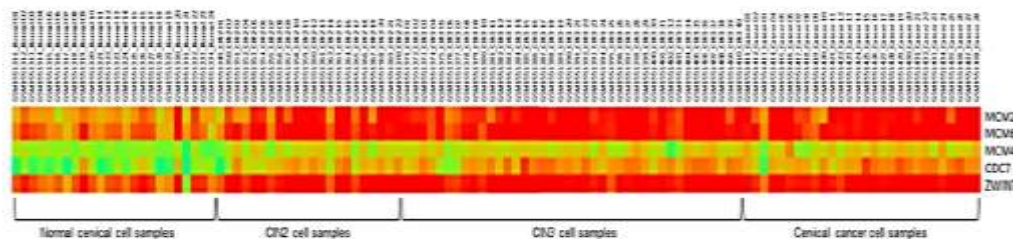


Fig. 6: Visualization with a heatmap to illustrate the increases of ZWINT expression along with increasing the disease stage or severity.³⁰

Its expression continues to increase along with increasing the disease severity, from CIN 2, CIN 3 to cancer, compared to normal cervical samples.³⁰

CONCLUSION

MMP1, EFNA1, ANLN and ZWINT expressions, especially MMP1, have the potential to be a diagnostic component for assessing progression and percentage of survival rate for cervical cancer sufferers. From all of the researches showed the same results that the higher genes expression, the worse the prognosis will be and the lower the survival rate in years ahead than in the group with lower and normal expression levels.

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