Expression and significance of erbB3 and erbB4 in cervical carcinoma

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Abstract **objective** To explore the expression and significance of erbB3 and erbB4 in cervical carcinoma. **Methods** Expression of erbB3 and erbB4 were examined by immuno-histochemical staining in 50 cases of cervical carcinoma, including 25 cases with adenocarcinoma and 25 cases squmous-cell carcinoma, 15 cases with normal cervical squamous epithelium. **Results** Expression of erbB3 and erbB4 were significantly higher in cervical carcinoma than that in normal tissue ($P < 0.05$); There wasn't significant statistically difference in squamous carcinoma than those in adenocarcinoma. ErbB3 and erbB4 protein were negative related to cell differentiation ,but positive correlation existed between erbB3 and FIGO stage. There was no significant correlation between the expression of erbB3 and erbB4 and prognosis of cervical carcinoma. **Conclusion** erbB3 and erbB4 can predict malignant potentiality, but they aren't possibly viewed as independent marker evaluating prognostic in cervical carcinoma .

Key Word cervical carcinoma; erbB3; erbB4; expression of gene protein

Epidermal growth factor receptor family took on activity of tyrosine protein kinase(TKA) , their overexpression may lead to cell degeneration, tumor occurrence and development. They were protooncogene with high research and application value [1,2]. ErbB3 and erbB4 were new members in the family and they were very homogeneity comparing to the other both members (EGFR、HER-2), However, there was few report about them in cervical carcinoma [3]. The study explored expression and significance of erbB3 and erbB4 in 50 cases cervical carcinoma, including 25 cases with squamous- carcinoma and 25 ademocarcionma respectively and 15 cases with normal cervical epithelial tissue.

MATERIALS AND METHODS

Materials

From January 1990 to December 1995, 50 cases with cervical carcinoma (25 cases with squmous cell carcinoma and 25 cases with adenocarcinoma), diagnosed by histopathologic examination, were retrieve form the first hospital of Xi'an medical university. Their average age was 44.5 years old (range 23~73). FIGO stage: stage Ⅰ, Ⅱ, Ⅲ, Ⅳ were15 cases, 24 cases, 9 cases and 2 cases respectively. Besides, 15 samples with normal cervix tissue were used as control group.

Methods

Expressions of erbB3, erbB4 gene protein were examined by immunohistochemical dyeing (reagent tube came from BoShiDe company, WuHan). Dilution concentration of the first antibody for erbB3 and erbB4 was 1:75 and 1:50 respectively. Operation method for experiment was carried out according to instruction of test kit.

Assessment of results

Positive cell was those whose cytoplasm was dyed yellow in immunohistochemical dyeing. Successive 5-high-field of vision were observed, positive result of immuno-histochemical were depended on dyeing density and number, over 10% of positive cells were defined as positive reaction and less 10% of positive cells were defined as negative reaction.

Statistics methods

Differences in proportion were evaluated by the x^2 or the Fisher test and Mean comparison by Wilcoxon test. Survival rate was calculated by survival curve and life-table.

RESULTS

Expression of erbB3, erbB4 in cervical carcinoma

Inmmuno-reaction mainly in cytoplasm, few confusing in member or cytoplasm and occasionally in cell nucleus. Their expression in squamous cell carcinoma was higher than that in adenocarcinoma (for erbB3 52.5% Vs 44.1% and for erbB4 44.0% Vs 36.0%), however, there was no statistic significance between them. In addition, positive rate was significantly higher in carcinoma than that in normal cervix tissue(latter expression for

Table 1 expression of erbB3, erbB4 and pathologic-parameter

	ErbB3			erbB4		
	n	-	+（%）	n	-	+（%）
Age (years old)						
<35	18	9	9(50.0)	8		8(44.4)
≥ 35	32	16	16(50.0)	24		10(31.3)
FIGO stage						
Ⅰ	15	12	3(20.0*)	13		2(13.3*)
Ⅱ	21	11	10(47.6)	14		7(33.3)
Ⅲ-Ⅳ	14	3	11(78.6)	3		11(76.9)
Tumor size						
<3cm	23	15	8(34.8)	17		6(26.1)
≥ 3cm	27	13	14(51.9)	16		11(40.7)
lymph node metastasis						
yes	14	7	7(50.0)	9		5(35.7)
no	36	20	16(44.4)	25		11(30.6)
differentiation grade						
Ⅰ	8	6	2(25.0*)	7		1(12.5*)
Ⅱ	24	13	11(45.8)	17		7(29.2)
Ⅲ	18	3	15(83.3)	5		13(72.2)

note： * P〈0.05

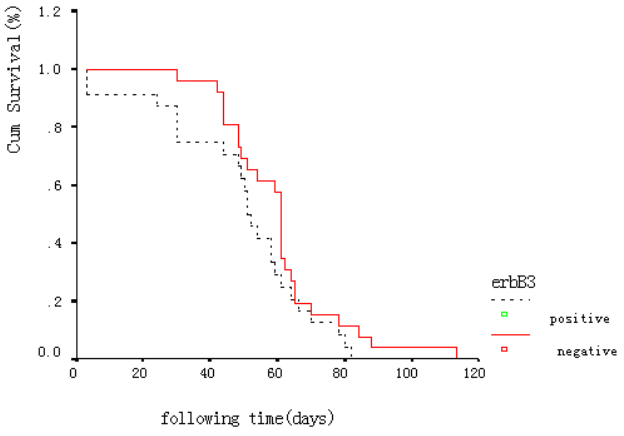

fig.1 survival curve between erbB3 expression and prognosis

erbB3, erbB4 were 10.0% and 0.0% respectively，P<0.05). Simultaneous expression for erbB3, erbB4 existed in 17 cases and no expression in 23 cases with cervix carcinoma tissue samples. Positive correlation existed between erbB3 and erbB4（r=0.5872，P<0.001）.

Expression of erbB3, erbB4 related to prognosis of cervical carcinoma and clinic–pathologic parameters

Positive correlations were found between erbB3 and erbB4 and cell grade and FIGO stage and there was no association between their expression and other clinic-pathologic parameters and prognosis (see table 1). Figure 1 showed both survival curves. The curve showed that low expression or no expression had better prognosis than high expression group. However, there was no statistic significance (P>0.1).

DISCUSSION

Epidermal growth factor receptor family was transmembrane glycoprotein taking on PTK activity and mainly located in cell membrane, However, the study showed that their immune-response was chiefly in cell plasma, few in cell membrane. These phenomena could concern receptor metabolism, recirculation and degradation[4]. As for as distribution way, erbB3 or erbB4 mainly took on diffuse, few on local reaction. Its mechanism wasn't clear and this might suggest tumor tissue contain different conversion cell strain, at the same time; this could reflect idiotype manifestation of immune phenotype. Higher expression of erbB3 or erbB4 in carcinoma than that in normal cervix tissue and this suggested they could play a part in occurrence of cervical carcinoma.

As for as expression of erbB3, erbB4 related to prognosis of cervical carcinoma and clinic-pathologic parameters. The study showed that positive correstion between erbB3 or erbB4 and cell grade and FIGO stage

and there was no association between their expression and other clinic-pathologic parameters and prognosis and this was coincidence with the report of Junn-Liang Chang[5]. This suggested erbB3 or erbB4 might only do with cell differentiation; however, they couldn't be viewed as useful marker predicting prognosis of cervical carcinoma.

REFERENCE

1. Friess H, Fukuda A, Tang WH, et al. Concomitant analysis of the epidermal growth factor receptor family in esophageal cancer: over-expression of epidermal growth factor receptor mRNA but not of erbB2 and erbB3. World J Surg, 1999, 23 (19):1010-1018.
2. Mitsuhashi A, Tanaka N, Suzuka K, et a. Detection of epidermal growth factor receptor mRNA in peripheral blood of cervical cancer patients. Gynecol Oncol, 2003, 89(3):480-485.
3. Bei R, Pompa G, Vitolo D, et al. Co-localization of multiple ErbB receptors in stratified epithelium of oral squamous cell carcinoma. J Pathol, 2001, 195(3):343-348.
4. Radhika Srinivasan, Cheryl E, Gillett, et al. Nuclear expression of the C-erbb-4/HER-4 growth factor receptor in invasive breast cancer. Cancer Rev, 2000, 60(15):1483-1487.
5. Junn-Liang Chang, Yeou-Ping Tsao, Dai-Wei Liu, et al . The expression of type 1 growth factor receptors in the squamous neoplastic changes of uterine cervix. Gynecologic Oncology, 1999, 73(1): 62-71.