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EXPRESSION OF C-MYC PROTO-ONCOGENE IN PREMALIGNANT AND MALIGNANT UTERINE CERVIX LESIONS

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EKSPRESIJA C-MYC PROTO-ONKOGENA U PREMALIGNIM I MALIGNIM PROMENAMA GRLIĆA MATERICE

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ABSTRACT

The aim of the study was to assess the expression and clinical significance of C-myc proto-oncogene in the progression of cervical neoplasms.

To establish the role of this proto-oncogene in uterine cervix carcinogenesis, we examined 69 tissue samples of: low grade cervical squamous intraepithelial lesions (SIL) (n=16), high grade SIL (n=11), portio vaginalis uteri (PVU) carcinoma in situ (n=11) and PVU invasive carcinoma, stage IA-IIA (n=13) (study group) and 18 samples without SIL or malignancy (control group), between January 2004 and December 2005. Expression of C-myc was detected immunohistochemically using monoclonal antibodies. Fisher's exact test was used to assess statistical significance. Sensitivity and specificity of the test, are higher and qualify the test as possible screening method for early detection of changes in the uterine cervix.

In our study, overexpression of C-myc oncogene was found only in patients with PVU invasive carcinoma (3/13–23.0%). Significant difference was not found in the frequency of overexpression in patients with PVU invasive carcinoma in relation to the control group (Fisher's test; p=0.064). The method's sensitivity of determining this oncogene with the aim of detecting PVU invasive carcinoma was 23% while specificity was 72.2%. We confirmed in our research that expression of C-myc oncogenes was increased only in patients with PVU invasive carcinoma. However, a more extensive series of samples and additional tests are required to establish prognostic significance of C-myc in cervical carcinogenesis.

Key words: C-myc proteins, immunohistochemistry, carcinoma, cervix utery.

SAŽETAK

Cilj ove studije je da ispita ekspresiju i klinički značaj C-myc proto-onkogena u progresiji cervikalnih neoplazija.

Da bi utvrdili ulogu ovog onkogena u karcinogenezi grlića materice, između Januara 2004. i Decembra 2005. ispitivali smo 69 uzoraka tkiva od čega: Low grade SIL (n=16), High grade SIL (n=11), Ca PVU in situ (n=11) i Ca PVU invasivum gradus Ia-IIa (n=13) (eksperimentalna grupa) a18 uzoraka bez SIL ili malignih promena na grliću materice (kontrolna grupa). Ekspresija C-myc onkogena je utvrđivana imunohistohemijski, korišćenjem monoklonskih antitela. Za ispitivanje statističke značajnosti je korišćen Fisher-ov test (p<0.05). Utvrđivanjem senzitivnosti i specifičnosti testa, nivo pouzdanosti ovih analiza je korišćen kao moguća skrining metoda za ranu detekciju promena na grliću materice.

U našoj studiji pozitivna ekspresija C-myc onkogena je pronađena samo kod pacijentkinja sa Ca PVU invasivum (3/13–23.0%). Analizom učestalosti pozitivne ekspresije C-myc onkogena između kontrolne grupe i pacijentkinja sa ca PVU invasivum, nije pronađena statistički značajna razlika (p=0.064). Senzitivnost metode određivanja ovog onkogena u cilju dijagnostikovanja invazivnih promena na grliću materice je 23%, a specifičnost 72.2%. U našim istraživanjima smo utvrdili da ekspresija C-myc onkogena je povećana samo kod Ca PVU invasivum.

Potrebne su međutim mnogo veće serije uzoraka da bi se utvrdio prognostički značaj ovog onkogena u karcinogenezi grlića materice.

Ključne reči: C-myc proteini, imunohistohemija, karcinom, grlić materice.

INTRODUCTION

Carcinogenesis is known to involve aberrant expression of genes involved in cell proliferation and differentiation. In mammalian cells, several independent lines of evidence have implicated the proto-oncogene C-myc in the control of cell proliferation and entry into the cell cycle (1). This gene was discovered as a cellular homologue of the transforming oncogene of avian viruses (2) and its product was subsequently found to be activated in various human cancers, including lung, breast, colon and uterine cervix (3, 4). The theory that C-myc acts as a central oncogenic switch in human cancers has been demonstrated by the ability of the oncogenic viral V-myc gene to induce rapid development of a variety of tumors in infected chickens (5). Chlamydia trachomatis and HPV high-risk types may contribute to neoplastic changes in the transformation of uterine cervix and also might modulate expression of C-myc oncogene (6). The C-myc gene belongs to the myc family that includes B-myc, L-myc, N-myc and S-myc. However, only C-myc, L-myc and N-myc have neoplastic potential (7). The ability of myc to promote cell proliferation indicates that its de-regulation leads to de-regulated DNA synthesis and genomic instability (8). De-regulated myc expression is linked to increase in both cyclin A and cyclin E levels (9). Many studies demonstrated that poor prognosis is in positive correlation with the expression degree of this oncogene (ovarium, uterus, cervix, lungs, prostate, breast, colon) (10–13). Amplification and/or overexpression of C-myc gene were frequently found in the advanced stages of cervical cancers and were shown to be associated with tumor progression (14, 15) and with aggressive, poorly differentiated phenotype. Moreover, myc overexpression was related to a 6.1 time higher risk of distant metastases suggesting that activation of this proto-oncogene may lead to the greater metastatic ability of tumor cells (16). A different distribution of myc expression has been reported in premalignant SIL lesions. While several studies have demonstrated that higher myc expression was positively related to all stages of pre-can-

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