

Immunotargeting of human cervical carcinoma xenograft expressing CA IX tumor-associated antigen by ^{125}I -labeled M75 monoclonal antibody*

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The aim of our present study was to explore a potential use of ^{125}I -labeled murine monoclonal antibody M75 that recognizes carbonic anhydrase IX (CA IX) in the immunotargeting of human cervical carcinoma xenografts in nude mice. CA IX is a hypoxia-inducible antigen, whose expression is significantly associated with carcinomas of the uterine cervix, whereas normal cervical tissue does not express CA IX protein. M75 monoclonal antibody was labeled with ^{125}I and used to quantify hypoxic induction of CA IX expression *in vitro* in HeLa human cervical carcinoma cells by immunoradiometric assay. HeLa cells showed inducible expression of CA IX *in vitro* by hypoxia (0.1% O_2) and various hypoxia mimicking agents (Co^{2+} , Ni^{2+} , Mn^{2+} , desferrioxamine, o-phenanthroline and $\text{Na}_2\text{S}_2\text{O}_4$). CA IX expression was also upregulated in the centre of HeLa multicellular clusters (spheroids) corresponding to the conditions of chronic hypoxia. For the immunotargeting study, ^{125}I -M75 was intravenously injected into immunodeficient mice bearing HeLa cervical carcinoma xenografts. Biodistribution profile showed selective and preferential accumulation of ^{125}I -M75 mAb in CA IX expressing HeLa xenografts in comparison with control unreactive ^{125}I -T111 antibody. Specificity was also confirmed by low uptake in CA IX negative C33A xenografts. In addition, CA IX expression in cervical carcinoma xenografts was analyzed by immunohistochemistry with M75. Detailed immunohistochemical analysis of HeLa xenograft sections revealed perinecrotically intensified expression of CA IX.

These results indicate that M75 mAb, recognizing CA IX antigen, has targeting properties which could be potentially useful in radioimmunodetection or radioimmunotherapy of human cervical carcinomas and derived metastases.

Key words: CA IX, cervical cancer, biodistribution, hypoxia, tumor targeting, M75 monoclonal antibody.

Cervical carcinoma is one of the most common cancer of women's reproductive tract. It represents a worldwide problem, causing 190,000 deaths yearly, with highest incidence in women living in developing countries [33].

Effective treatment of cervical cancer requires precise staging of a malignant lesion. Several examinations of the abdomen and pelvis, such as ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), lymphangiography, etc. are used for evaluation of anatomic extent of tumor infiltration. Examinations based on radioimmunodetection of cervical cancer may provide efficient choice for noninvasive radiologic staging. Radiolabeled monoclonal antibodies

(mAbs) selective for tumor-associated antigens have been effectively used in several clinical studies for radioimmunodetection of tumors by radioimmunoscinigraphy and for radioimmunotherapy with certain antitumor response [8]. Utilizations of mAbs in immunotargeting, resp. radioimmu-

Abbreviations: BSA – bovine serum albumin; CA IX – human carbonic anhydrase IX protein; CA9 – human carbonic anhydrase 9 gene; CIN – cervical intraepithelial neoplasia; CT – computed tomography; DFO – desferrioxamine; FIGO – staging nomenclature of the International Federation of Gynecology and Obstetrics; HIF1 α – hypoxia-inducible factor 1 α ; %ID/g – uptake; mAb – monoclonal antibody; M75 – CA IX specific monoclonal antibody; LET – linear energy transfer; MRI – magnetic resonance imaging; oPE – o-phenanthroline; PBS – phosphate buffered saline; PET – positron emission tomography; pVHL – protein product of von Hippel-Lindau gene; RBE – relative biological effectiveness; SDS-PAGE – sodium dodecyl sulfate-polyacrylamide gel electrophoresis; VEGF – vascular endothelial growth factor.

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