Abstract

Changes in the expression and presentation of antigens during progression of experimental tumours associated with Human papilloma virus 16; analysis of defects and their influence on imune response

Loss or downregulation of MHC class I molecules on tumour cells is an important mechanism which enables tumours to escape from T-cell mediated immune response. This type of evasion can be found in cervical carcinoma (CC) which is associated with Human papilloma virus 16 (HPV16). To ascertain why the alterations in MHC class I expression occurred, different cell lines with distinct surface expression of MHC class I molecules mimicking CC were used. As the results from RT-PCR and qRT-PCR showed, the changes were not ascribed to irreversible mutations in genes encoding for MHC (H-2D^b, H-2K^b, β_2m) but were associated with silencing of expression of certain APM genes at the transcriptional level, namely TAP-1, TAP-2, LMP-2, LMP-7 and tapasin. It is known that these defects can be reversed by the addition of cytokines (IFN-γ and TNF-α) or epigenetic agents. TC-1/A9, a cell line with no detectable MHC class I surface expression, showed increased expression of these molecules after cultivation with epigenetic agents. Flow cytometry was used to specify surface expression of costimulatory CD80 molecules and adhesive CD54 molecules due to their importance in CTL activation and interaction with APC or target cells. The expression level of MHC class I, CD80 and CD54 determine the type of antitumour immune response. The tumour cells expressing the aforementioned molecules can be recognized by CTL while NK cells are recruited against tumour cells lacking the molecules although other immune mechanisms can not be excluded.

In vivo experiments showed that the phenotype of the tumour cells changed during tumour growth. The main changes in expression of surface molecules occured in the early phase of tumour development when the size was to small to analyse. Viral antigens E6 a E7 were not lost which was a positive result since most of experimental therapeutical vacciness against HPV tumours target these oncoproteins. The importance of E6 and E7 expression in regard to experimental cell vaccines was proved in another *in vivo* experiment. Immunization with a cell line without MHC class I molecules derived from RSV (Rouse sarcoma virus), therefore lacking E6 and E7 expression, did not suppress the growth of HPV tumours with the same MHC class I phenotype expressing E6 and E7 oncogenes.

Klíčová slova: HPV16, nádory, MHC molekuly I. třídy, cytotoxické T lymfocyty, NK buňky, nádorové antigeny, epigenetika, protinádorové vakcíny

Key words: HPV16, tumours, MHC class I molecules, cytotoxic T lymphocytes, NK cells, tumour antigens, epigenetics, antitumour vaccines