Editorial

MHC Class I Downregulation, Tumour Escape from Immune Surveillance and Design of Therapeutic Strategies

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Most of recent human immunotherapy stategies are based on the activation of MHC class I-restricted mechanisms such as $CD8^+$ cytotoxic T lymphocytes (CTLs). However, malignant conversion of mammalian cells followed by immune selection in tumour cell populations is frequently associated with the loss of function of MHC class I genes which were expressed in malignant cell precursors. The MHC class I downregulation results in decreased sensitivity of the tumour cells to MHC class I-restricted CTLs, the major component of the tumour rejection reaction. Due to cross-priming by MHC class I^- donors' dendritic cells, which can use their own MHC class I molecules for antigen presentation, in the peripheral blood of MHC class I^- tumour patients, the $CD8^+$ CTLs can be detected (Offringa et al., 2000). However, these CTLs cannot attack the MHC class I^- tumour cells and this can provide the explanation for the paradoxical detection of CTLs in the peripheral blood of vaccinated patients in spite of the absence of any clinical responses. Thus, the MHC class I restriction of the $CD8^+$ T cell-mediated immunity can provide the MHC class I^- tumours with a possibility to escape from immune surveillance. Therefore, the MHC class I status of the tumour to be treated by immunotherapeutic or immunomodulatory gene therapy strategies should be established prior to the decision which therapeutic protocol is suitable for the respective tumour patient. Unfortunately, this requirement is usually not respected and this may be one reason why in the majority of clinical tumour immunotherapy trials the complete and partial responses have been found to be rather rare.

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Abbreviations: CTLs – cytotoxic T lymphocytes, DCs – dendritic cells, IFN – interferon, IL – interleukin, MHC – major histocompatibility complex, NK – natural killer, TNF – tumour necrosis factor.

Several types of MHC class I defects have been described in human tumours, including total, locus, allele and haplotype loss. These defects are either irreversible, such as β_2 microglobulin and class I heavy chain gene disabling mutations, or reversible. The reversible MHC class I defects involve all levels of the MHC class I-restricted antigen presentation machinery and can be repaired by various therapeutic procedures (for a review, see Garrido et al., 1997; Hicklin et al., 1999; Bubeník et al., 2003a, b, 2004). For instance, inteferons (IFNs) and tumour necrosis factor alpha (TNFα) were shown to be capable of upregulating MHC class I expression in both normal and neoplastic cells. However, although TNFα may enhance the expression of the MHC class I molecules, it does not always induce MHC class I molecule expression in MHC class I^- neoplasms (Pfizenmaier et al., 1987; Singer and Maguire, 1990).

MHC class I molecules downregulation helps tumour cells evade the conventional T cell-dependent immune responses. It simultaneously imposes another, the natural killer (NK) cell-mediated surveillance, stimulated by the "missing self" (Ljunggren and Kärre, 1990) signal. The innate and adaptive antitumour immunity may be interconnected. The primary activation of the MHC class I-unrestricted surveillance mechanisms may lead to the production of IFNγ by the activated NK/γδ T cells; the *in situ* produced IFNγ may then upregulate the MHC class I expression on the tumour cell surface and in this way stimulate the more efficient, MHC class I-restricted, concomitant immunity (Bubeník, 2004).

Despite the MHC class I downregulation and the resulting resistance to the $CD8^+$ CTLs, the tumour hosts have been successfully immunized against various experimental tumours, such as malignant melanoma, HPV16-associated carcinoma and colon adenocarcinoma. Moreover, the tumour-inhibitory effects were observed with these tumours after gene therapy with IL-12-transduced or IL-2-transduced tumour vaccines, after cytokine therapy with IL-2 and IL-12, or after peritumoral administration of IFNγ (for a review, see Bubeník, 2003b). Various mechanisms were reported to operate in these experimental tumour systems, such as NK cells, NK cell-mediated antibody-dependent cellu-

lar cytotoxicity, lymphokine-activated killer cells and $CD4^+$ T cells. Both, direct and indirect effects of the cytokines were involved. IL-12, in addition to enhancing dendritic cell (DC) function, could display its direct antiangiogenic properties, stimulation of IFNγ production by NK cells, and stimulation of TNFα production. IL-2 could enhance IFNγ production by both T and NK cells and, simultaneously, DCs from tumour host bone marrow could activate $CD8^+$ and $CD4^+$ T cells due to the cross-priming. The IFNγ could upregulate MHC class I molecule expression on the tumour cell surface and, in this way, induce sensitivity of the tumour cells to the MHC class I-restricted imunity (for a review, see Bubeník, 2003b; Bubeník and Vonka, 2003).

It may be envisaged that the elaboration of tumour immunotherapy and immunomodulatory gene therapy protocols in the near future will differ in patients carrying MHC class I^+ and MHC class I^- tumours. In patients with MHC class I^- tumours it will be important to learn whether their tumour MHC class I deficiency can be repaired *in vitro* with IFNγ (defects of TAP-1 and TAP-2, LMP-2 and LMP-7, MECL-1, PA 28). In such tumour cases the cytokine therapy with exogenous IFNγ, IL-12, IL-2 or with tumour vaccines carrying the respective inserted cytokine genes and producing the cytokines should be considered.

An additional problem can be imposed by the question whether the immune escape phenotype is stable or whether the MHC class I molecule expression can change during tumour progression and therapy. It has been found that the immunoselective pressure, the concomitant imunity accompanying the growth of the MHC class I^- tumour in its host can lead to upregulation of MHC class I expression if the tumour has a reparable MHC class I defect. This upregulation is apparently due to the production of IFNγ in the tumour microenvironment and its vicinity (Mikyšková et al., 2003, 2005). Similar upregulation of the MHC class I molecules expression was found after irradiation of the tumour cells mimicking *in vivo* radiotherapy of MHC class I^- tumours, and in tumour recurrences after surgery. The upregulation observed in the recurrences after surgery or after irradiation has reached a level required for *in vitro* cytolysis of the tumour cells by $CD8^+$ CTLs (Bubeník, 2004). Even higher MHC class I upregulation and substantial inhibition of tumour growth has been observed after peritumoral administration of IFNγ. These effects of IFNγ were inhibited by anti-IFNγ antibodies (Mikyšková et al., 2003; ibid., 2005). These results suggest that, at least in some MHC class I^- tumours with IFNγ-reparable MHC class I defects, the immune escape phenotype is not stable, that it can be reverted during tumour progression and therapy, and that these findings should also be considered in future when elaborating the tumour immunotherapy and immunomodulatory gene therapy protocols.

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