Editorial

Genetically Modified Vaccines Augment the Efficacy of Cancer Surgery and Chemotherapy

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Local recurrences at the site of tumour resection or after chemotherapy as well as distant micrometastases represent major problems in oncology. Therapeutic strategies based on insertion of immunostimulatory genes into the genome of tumour cells followed by vaccination with the resulting, genetically modified and irradiated cellular vaccines bring a new potential prospect for treatment of cancer patients and can hopefully help, at least in some cases, to augment the efficacy of the conventional cancer treatment (Bubeník, 1996a, b). With regard to the metastases, the vaccination approach is based on the presumption that local treatment of primary tumours can, thanks to its immunizing potential, also result in the inhibition of metastases. The genetically modified cellular vaccines were found to be efficient against cancer both in experimental tumours (Bubeník, 2008) and in cancer patients (Russel et al., 2008). It was shown in various models that the efficacy of conventional therapeutic modalities can be supported by adjuvant local administration of genetically modified vaccines in the vicinity of the tumour (Vlk et al., 1998; for a review see Bubeník and Šímová, 2005); the effect of the adjuvant administration can be illustrated in the experimental system of human papillomavirus type 16 (HPV16)-associated tumours.

Therapeutic genetically modified tumour vaccines were for the first time utilized for treatment of HPV16-associated neoplasms in preclinical studies a decade ago (Bubeník et al., 1999). Genes for immunostimulatory cytokines (IL-2, IL-12, GM-CSF) were inserted into the genome of murine tumour cells established by co-transfection with HPV16 *E6/E7* and activated (G12V) human Ha-*ras* oncogene DNA (Indrová et al., 2001; Bubeník et al., 2003; Indrová et al., 2006; for a review see Bubeník, 2008), and the resulting vaccines were utilized for adjuvant treatment of residual tumour disease after surgery (Bubeník et al., 1999; Šmahel et al., 2001; Indrová et al., 2002; Bubeník, 2006a) or chemotherapy (Indrová et al., 2003; Mikyšková et al., 2004). It has been found that administration of the genetically modified, cytokine-producing tumour vaccines substantially reduced the percentage of tumour recurrences and inhibited tumour growth (for a review see Bubeník and Šímová, 2009). It has also been found that local IL-2 treatment of mice after surgery of HPV16-associated tumours reduced the percentage of tumour recurrences as well as the number of lung metastases (Mikyšková et al., 2001). The vaccines producing GM-CSF were substantially less efficient than those producing IL-2 and IL-12. Since the vaccines producing IL-2 could also support the efficacy of immunosuppressive T-regulatory (Treg) cells (Bubeník, 2006b) in addition to the tumour-inhibitory effector cells, the vaccines producing IL-12 were chosen as the optimal solution. In addition to their tumour-inhbitory effects, these vaccines were also able to decrease the immunosuppressive efficacy of immature myeloid cells, the number of which increased after treatment with some chemotherapeutics; these vaccines also repaired the absence of cytotoxic and proliferative response of tumour-infiltrating cells after chemotherapy. Similar results were obtained in experimental leukaemia systems (Bubeník et al., 1995a, b; Sobotková et al., 2009) and in some phase II–III clinical trials (for a review see Cross and Burmester, 2004). Taken collectively, the above data indicate that adjuvant immunomodulatory gene therapy can substantially improve the efficacy of surgical treatment in preclinical cancer models as well as in selected clinical trials. The efficacy of the adjuvant gene therapy is dependent on many variables, such as the vaccine, time window for therapy (Vlk et al., 1998) and the tumour residuum itself. Many technical problems must still be solved prior to the development of the optimized individual therapeutic protocols, but the rationale of the adjuvant therapy of residual tumour disease with genetically modified tumour vaccines, the enhancement of the antitumour immune reaction that helps eradicate the minimal residual tumour foci, is supported by the above data. The adjuvant immunomodulatory gene therapy modalities have the same limitations as the immunotherapy itself. The success depends on the results of tumour editing prior to surgery or chemotherapy (Mikyšková et al., 2005), immunogenicity and immunosensitivity of the tumour residua, as well as immunosuppressive cells and substances present in the tumour microenvironment (Bubeník, 2006b). The crucial diference between the gene therapy of bulky and generalized tumours and the minimal residua after sur-

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gery or chemotherapy is the favourable effector/target cell ratio in the residua and the removal of the "immunosuppressive" tumour mass. However, more information on the tumour phenotype and the immune reaction profile of the patients must be collected prior to the design of the therapeutic protocols in individual cancer cases (Bubeník and Šímová, 2005).

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