The impact of IL-10 concentration reduction in the tumor microenvironment on the effectiveness of cyclophosphamide and dendritic cell-based therapy in the MC38 murine colon carcinoma

Application of dendritic cell-based vaccines in immunotherapy enables the generation of a specific antitumor response. However, the accumulation of immunosuppressive factors, which hinder the activation of immune mechanisms in the tumor microenvironment (TME), significantly lowers the therapeutic potential of dendritic cells. As a result, considerable efforts are being taken to develop combined therapies, where cell-based vaccines are used in conjunction with anti-immunosuppressive agents. In the TME, interleukin-10 (IL-10) is responsible for inducing immunosuppressive cells, as well as inhibition of secretion of proinflammatory cytokines and maturation of dendritic cells. As these processes invariably lead to tumor progression, IL-10 is regarded as a potent target for combined therapies.

The aim of this study was to determine the effects of reduction of IL-10 concentration in the TME on the efficiency of chemoimmunotherapy composed of cyclophosphamide (CY) and dendritic cells stimulated with tumor antigens (BMDC/TAg) in MC38 murine colon carcinoma model. In course of the experiments, 3rd generation lentiviral vectors encoding shRNA that binds IL-10 mRNA (LV shIL-10) were used to silence the expression of IL-10 in target cells.

The research showed that intratumorally injected LV shIL-10 vectors are efficient shRNA carriers and that they reduce the amount of IL-10 secretion in MC38 tumors. Following the immunotherapy, where LV shIL-10 vectors and vaccines containing BMDC/TAg were distributed three times at weekly intervals, a significant tumor growth inhibition was observed. Reduced expression of IL-10 resulted in increased differentiation level of tumor-infiltrating myeloid cells, accompanied by the influx of T CD4$^+$ and T CD8$^+$ lymphocytes. Furthermore, the therapy caused the stimulation of the systemic antitumor response. Extending the protocol by a single administration of an immunomodulating dose of CY further improved the results of the immunotherapy. Chemoimmunotherapy with CY increased the influx of T CD4$^+$ and T CD8$^+$ lymphocytes, as well as NK and NKT cells, while lowering the percentage of immunosuppressive cells in MC38 tumors. Changes in the TME were reflected in stimulation of both local and systemic Th1-type response.

The presented results prove that the reduction of IL-10 levels in the TME combined with immunomodulation using CY increases the efficiency of dendritic cell-based vaccines and leads to the induction of a specific antitumor response.