Effect of dendritic cells transduced with lentiviral IL-12 and IL-18 gene carriers for activation of anti-tumor response in murine MC38 colon carcinoma model

Abstract

The application of dendritic cell (DCs)-based vaccines in anti-tumor therapy enables enhancing the reactivity of the immune system in cancer patients. In order to increase their efficiency, attempts are made to modulate of DC properties. One of the methods developed for modifying these cells is their *ex vivo* stimulation with tumor antigens (TAg). Significant factors involved in the upregulation of the anti-tumor response are cytokines, e.g. interleukin (IL-) 12 and IL-18 which induce the activation of cytotoxic T lymphocytes and NK cells, contributing to tumor growth delay.

The aim of this study was to develop and determine the effect of the application of dendritic cell-based vaccines transduced for the production of IL-12 and/or IL-18 and stimulated with tumor antigens on the induction of anti-tumor response in the MC38 mouse colon carcinoma model.

Dendritic cells transduced with lentiviral vectors carrying IL-12 or IL-18 genes and stimulated with tumor antigens turned out to be capable of increased production of IL-12 (DC/IL-12/TAg) or IL-18 (DC/IL-18/TAg), or both of these cytokines simultaneously (DC/IL-12+IL-18/TAg) as well the activation of specific *ex vivo* anti-tumor response. Moreover, modified DCs secreting cytokines, especially DC/IL-12+IL-18/TAg, were characterized by an increased ability to infiltrate tumor tissue, whereby a single peritumoral administration of these cells had the potential to activate a local anti-tumor response. Such characterized vaccines containing modified DCs have been used for anti-cancer therapy in the mouse MC38 colon carcinoma model. It was found that the repeated administration of DC/IL-12+IL-18/TAg generated a short-term therapeutic effect related to changes in the tumor microenvironment and activation of the systemic immune response. However, combined therapy with cyclophosphamide and DC/IL-12+IL-18/TAg led to prolonged inhibition of MC38 tumor growth. It was associated with an increase in the size of the effector T lymphocyte and NKT cell population, a decrease in the percentage of Treg and TAM cells in tumor tissue, and strong induction of a systemic anti-tumor response.

The results presented in this study show that only chemoimmunotherapy with vaccines based on dendritic cells transduced for the simultaneous production of IL-12 and IL-18 and stimulated with tumor antigens can intensify and significant prolongation of the specific antitumor response. This observation suggests the high potential for using the proposed combination therapy in the fight against solid tumors.