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Toll Like Receptor 7/8 agonists antitumor effects on NK cells in murine melanoma model

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Abstract

Background: Toll-like receptors (TLRs) are a subclass of molecules that regulate both innate and adaptive immune cells, and this ability makes them attractive targets for cancer immunotherapy. Synthetic TLR agonists, such as imidazoquinolines, activate TLR7/8 receptors on various immune cells and offer exciting perspectives for cancer therapy.
Aim: In this study we aimed to investigate the effects of TLR7/8 agonists, imiquimod and gardiquimod, on NK cell phenotype and tumor growth in a mouse model of melanoma.
Methods: C57BL/6J mice were injected subcutaneously with B16-F10 melanoma cells on day one. The TLR7/8 agonists used were imiquimod (IMQ), gardiquimod (GDQ) and imiquimod cream (ALDARA), and treatment was administrated after tumor development. IMQ and GDQ were administrated intratumorally on days 8, 10, 15, and 18, while ALDARA was applied topically starting on day 14, for 5 consecutive days. The untreated control group received phosphate-buffered saline solution. Tumor size was measured weekly to determine the impact of treatment. To examine the effects of TLR7/8 agonists on NK cells, mice were euthanized on day 21 and spleens were harvested and assessed immediately using flow cytometry analysis for NK cell surface markers. A control group of healthy mice was considered.
Results: ALDARA treatment induced significant inhibition of tumor growth, while no significant differences were observed in the IMQ and GDQ groups, except for one mouse that received GDQ. In this case, a tumor regression was observed and after two months the tumor started to grow. At necropsy, macroscopically visible melanoma metastases were observed on the lungs. A decrease in the percentage of NK1.1+ and CD49+ cells in the spleen was observed in all groups compared with healthy mice. Evaluation of NK cell phenotype showed an increase of CD69+ and B220+CD11c+NK1.1+ cells in all treated groups. Analysis of NK cell subsets indicated a decrease of the mature cell subset and an increase of the immature cell subset in tumor-bearing mice, with or without treatment, except for the ALDARA treatment group.
Conclusions: Our study showed that treatment with TLR7/8 agonists induced a slowing of tumor growth and activated NK cells. These data can provide new insights into the knowledge of the NK cell phenotype and function in solid tumors treated with TLR7/8 agonists and also new approaches in cancer immunotherapy.