ABSTRACT

The adoptive transfer of T cells expressing chimeric antigen receptors (CARs) is an effective therapy, successfully applied recently in the treatment of hematological malignancies. However, the use of this approach is still limited in the treatment of solid tumors. One of the major challenges is the immunosuppressive environment at the tumor site, which impairs the effectiveness of CAR-T cells. Cancer cells prevent the immune attack by increasing the expression of immune checkpoint molecules, which serve them as natural “shields”. In particular, the immune checkpoint molecule programmed death-ligand 1 (PD-L1) is often selectively overexpressed on the surface of tumor cells and/or on the cells composing tumor microenvironment (TME). Thus, PD-L1 molecule is an attractive target for CAR-based therapy. In this study, the technology of primary human T cells modification with PD-L1-CAR was successfully implemented and optimized in our laboratory. The ability of modified PD-L1-CAR-T cells to recognize and attack PD-L1-expressing tumors was assessed using breast cancer cell lines with various levels of target protein expression. The non-malignant mammary cells were used to evaluate the safety of the PD-L1-CAR-based therapy. The obtained results indicate the efficiency of the PD-L1-CAR-T cells in the specific elimination of PD-L1-positive cells. Additionally, the CAR-bearing T cells were observed to induce PD-L1 expression on the surface of targeted cells, which demonstrates the self-amplifying mechanism of PD-L1-CAR-T cells action. Such a self-amplification phenomenon appears to be unique among the CAR-based strategies and can markedly broaden the potential spectrum of malignancies targeted with the PD-L1-CAR-based therapies. Concomitantly, the obtained data implies the potential cytotoxicity of the PD-L1-CAR-T cells towards non-malignant cells. In summary, the study demonstrates the feasibility of targeting breast cancer using PD-L1-CAR-T cells, while indicating, that this approach requires extensive caution in the introduction into clinical studies.