ABSTRACT

The immune checkpoint blockade is a novel approach of cancer therapy, which markedly enhanced treatment efficacy of several cancer types. However, the frequency of cancer patients non-responding to this treatment is high. Establishment of predictive markers to distinguish patients suitable for the immune checkpoint blockade would enhance the number of patients receiving benefit from the therapy. This dissertation thesis focuses on the enhancement of efficacy of immune checkpoint inhibitors (ICIs) and predictive markers in experimental models of mouse tumours induced by TC-1 and TC-1/A9 cell lines and its clones with deactivation of interferon (IFN)-γ signalling (TC-1/dIfngr1 and TC-1/A9/dIfngr1), or CD80 molecule (TC-1/dCD80-1). IFN-γ is presumed to be the main inducer of programmed death ligand 1 (PD-L1) and a major histocompatibility complex I (MHC-I). Moreover, PD-L1 expression may predict sensitivity to PD-1/PD-L1 blockade. Non-functional IFN-γ signalling or downregulated MHC-I expression has been associated with resistance to ICIs in some patients. We found that IFNs type I (IFN-α and IFN-β) induced the expression of PD-L1 and MHC-I on TC-1/A9/dIfngr1 tumour cells with reversible downregulation of both molecules. We also showed that deactivation of IFN-γ signalling in TC-1/A9 cells was not a contraindication to PD-1/PD-L1 blockade combined with DNA vaccination. As TC-1-induced tumours were not sensitive to PD-L1 blockade, we next investigated the impact of CD80 expressed in tumour cells on the efficacy of ICIs and the tumour microenvironment. Although the CD80 deactivation in tumour cells did not induce the efficacy of anti-PD-L1 antibody, it considerably promoted the efficacy of anti-CTLA-4 antibody. Moreover, TC-1/dCD80-1 cells were more immunogenic than the TC-1 cell line. Therefore, CD80 molecule should be assessed as a predictive marker for cancer treatment by CTLA-4 blockade and as a possible target for the development of tumour cell-specific cancer therapy. Besides the major projects, experimental combined therapy of tumours with reversible downregulation of MHC-I and development of mouse oncogenic cell line with irreversible downregulation of MHC-I by deactivation of beta-2-microglobulin (B2m) are included in the thesis. Altogether, we developed clinically relevant models of mouse tumours with deactivated IFNGR1, CD80, and B2m and used them for enhancement of cancer immunotherapy and for search of its predictive markers.