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Abstract

We established humanized mouse models by transplantation of human hematopoietic (stem) cells to immunodeficient mice. Engraftment results in the development of a functional human immune system. By co-transplantation of human patient-derived xenografts (PDX) we successfully generated a fully human tumor-immune-cell (TIC) model in mice. These humanized TIC-PDX models for melanoma and lung cancer were further characterized by treatment with immune therapy drugs like the CTLA4 inhibitor ipilimumab (Ipi) and the PD-1 inhibitor nivolumab (Nivo). In our current studies we monitored the effects of the human immune cells and evaluated concepts for combination therapies i.e. with chemotherapy or radiation. We further established new human TIC-PDX models from other tumor entities like lymphoma, pancreatic or breast cancer.

Hematopoietic stem cell engraftment was monitored by regular FACS analysis for human immune cells in the blood. PD-L1 expression on tumors as a target for immunotherapy was determined by FACS and immunohistochemistry. PD-L1 positive and negative PDX from 10 different entities were transplanted on humanized mice and treated with Nivo or Ipi alone or in combination therapy with radiation. Blood and tumor samples were analysed by FACS and immunohistochemistry for immune cell infiltration and activation.

The transplanted stem cells showed engraftment in immunodeficient mice with proliferation and differentiation and established a functional human immune system with T-cells, B-cells, NK-cells, monocytes, and dendritic cells. So far, we have transplanted more than 40 different PDX from 10 different tumor entities on humanized mice. Most of investigated PDX (>70%) successfully engrafted on humanized mice and showed no difference in tumor growth compared to growth on non-humanized mice. However, for a few PDX we observed a delayed tumor growth or a complete rejection. These results suggest an immune reaction of the engrafted human immune cells against the PDX. The tumor engraftment or rejection in the humanized mice seems to be independent from the tumor entity. To evaluate whether engraftment of the PDX in mice with a human immune system is in part enabled by checkpoint mediated immune-tolerance, we have treated over 30 PDX models with Ipi or Nivo alone or in combination. Significant tumor growth delay, observed in most models, accompanied by an increased number of T-cells in the blood and in the tumor, has functionally validated our immune-PDX model. Response to the checkpoint inhibitors seems to correlate with innate immune responsiveness and PD-L1 expression and can be further increased by combination with radiotherapy.

Our humanized immune-PDX models enable appropriate preclinical translational research in tumor immune biology and the evaluation of new therapies and combinations, as well as the identification and validation of biomarkers for immune therapy.