Preclinical Case Study: Patient-derived head and neck cancer xenograft on mice humanized with autologous immune cells
- a model for personalized immuno-oncology research

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Background and Aim

The preclinical evaluation of novel immune checkpoint modulators for cancer treatment remains a challenge, as models require both, engraftment of human tumor cells and a compatible human immune cell population. In previous experiments, we have demonstrated, that we can use either peripheral blood mononuclear cells (PBMCs) or hematopoietic stem cells (HSC) to establish a humanized immune system with functional T-, B-, and NK cells, monocytes, and dendritic cells on highly immunodeficient mice. However, these models are limited by rarely matching HLA isoatypes between tumor and immune cells.

In this case study, we established a patient-derived xenograft (PDX) model from a patient with Head and Neck squamous cell cancer (HNSCC). Furthermore, we used our humanized mice (HSC based) to investigate this model under immunotherapy.

Summary and Outlook

We developed a humanized immune PDX model enabling appropriate preclinical translational research on tumor immune biology and the evaluation of new therapies and combination, as well as the identification and validation of biomarkers for immune therapy. Furthermore, results showed a correlation between immune therapy effect and HLA matching in preclinical models, especially using PBMCs as cell source for humanization. Humanized mice based on HSC transplantation have to be further characterized and the correlation with the HLA-matching has to be investigated in detail.

Establishment and characterization of HN15239

- PDX of HNSCC was established by directly transplanting surgical material to immunodeficient mice
- xenografts are passed in vivo and stored as stock in liquid nitrogen

Effects on treated mice

- 4 treatment groups (3 - autologous PBMCs, C - allogenic PBMCs with different HLA match)
- transplantation of PBMCs 5 of 6 mice per group were treated with Nivolumab

Summary and Outlook

- HN15239 is chemosensitive to Cetuximab, Docetaxel, Paclitaxel and Cisplatin
- Cetuximab induced no tumor growth inhibition compared to the other treatments
- PDX model HN15239 showed a donor dependent tumor growth
- PBMCs with a high HLA match support tumor growth compared to non-humanized mice and to PBMCs with a lower HLA match
- treatment with Nivolumab induced a strong growth inhibition compared to non-treated mice in group with high HLA-match
- no treatment effects could be observed in combination with autologous PBMCs (patient of PDX is still under Nivolumab treatment in the clinic)
- IHC staining and FACS analysis showed infiltration of immune cells in autologous and allogenic settings

Patient-derived xenograft models on huHSC mice

- Humanized mice with hematopoietic stem cells (huHSC mice)
- Mice humanized with peripheral blood mononuclear cells (huPBMC mice)

Patient-derived xenograft models on huHSC mice

- Humanized mice models with immune cells and CDX/PDX - schematic overview
- Humanized immune deficient mice with CD34+ stem cells from cord blood (hHSC)

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