Translational studies of metastatic melanoma in the era of immunotherapy -From humanized mouse models to clinical trials

Avhandlingen baseras på följande delarbeten

   Clinical responses to adoptive T-cell transfer can be modelled in an autologous immune-humanized mouse model
   "Nature Communications. 2017 Sep 27;8(1):707"

   HER2 CAR-T cells eradicate uveal melanoma and T-cell therapy–resistant human melanoma in IL2 transgenic NOD/SCID IL2 receptor knockout mice
   "Cancer Research. 2019 Mar 1;79(5):899-904"

    Combined HDAC- and PD-1 inhibition in experimental and human melanoma.
    "Manuscript"
Translational studies of metastatic melanoma in the era of immunotherapy - From humanized mouse models to clinical trials

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Abstract
Immunotherapy with PD-1 inhibitors has transformed the treatment of metastatic cutaneous melanoma, and can lead to complete and durable responses in a proportion of patients. However, in around half of the patients, the treatment has little or no effect. In patients with metastatic uveal melanoma, a rare form of melanoma arising in the eye, effective treatments are lacking altogether. The overall aim of the research on which this thesis is based, is to develop and utilize mouse models to identify new immunotherapies for patients with metastatic melanoma.

In paper I we describe the development of a novel immune humanized patient derived xenograph (PDX) model. The PDX is based on sequential transplantation of ex vivo expanded, autologous tumor infiltrating lymphocytes (TIL), and mirror the treatment effects seen in corresponding patients. In paper II we evaluate the feasibility and preclinical efficacy of chimeric antigen receptor (CAR)-T cell therapy in melanoma and find that CAR T cells against HER2 are able to kill human cutaneous and uveal melanoma cells in vitro and in vivo. In paper III we first assess the rationale of combined epigenetic modulation and PD-1 inhibition in experimental melanoma, and show that the histone deacetylase (HDAC) inhibitor entinostat increases expression of HLA-I and PD-1 on melanoma cell lines and enhances the effect of a PD-1-inhibitor in vivo. Next, we describe the design and preliminary results of an ongoing phase II trial evaluating the effect of entinostat in combination with pembrolizumab (a PD-1 inhibitor) in patients with metastatic uveal melanoma.

In conclusion, this thesis shows that i) PDX models can be used to study key aspects of the human antitumoral immunity in melanoma; ii) that HER2 CAR-T cells represent a potential future treatment for metastatic melanoma refractory to other immunotherapies; and iii) that entinostat increases HLA-I expression and potentiates the effect of PD-1 inhibition in melanoma models, and that the same combination can result in clinical efficacy with manageable toxicity in patients with metastatic uveal melanoma.

Keywords: Metastatic melanoma, uveal melanoma, humanized mouse models, immunotherapy, chimeric antigen receptor T cells, PD-1 inhibition, epigenetics, histone deacetylase inhibition

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