Preclinical model of patient-derived tumor xenograft in humanized mice

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Background and Aim

The stimulation of the endogenous antitumor immunity has the potential to achieve clinically significant tumor regression. The recent clinical success with antibodies interfering with immune checkpoints on T cells (PD1 and CTLA-4) has motivated oncology research world wide to focus on new immunotherapy approaches. The identification and validation of new targets for antitumor immune therapy is still a challenge for the preclinical research as the classical syngeneic tumor models are of limited translational value and the patient-derived tumor xenograft models (PDX) are growing on immunodeficient animals.

To overcome these constraints our aim is the development of PDX models on mice with a functional human immune system to improve predictability of drug efficacy and safety.

Summary and Outlook

We reconstituted a functional human immune system by engrafting human hematopoietic stem cells in immunodeficient mice.

Repopulation of mouse organs with human hematopoietic cells and maturation of human T and B cells has been demonstrated.

Fragments from patient-derived melanoma were successfully engrafted on our humanized mouse models.

No evidence for tumor rejection was observed, although engraftment was accompanied by an increase of human T cells in the peripheral blood.

Treatment with the checkpoint-inhibitor ipilimumab decelerate the tumor growth in one of two tested humanized mouse models.

Accumulation of cytotoxic T cells were found in ipilimumab responsive tumors compared to ipilimumab non-sensitive tumors.

Treatment with the checkpoint-inhibitor nivolumab in combination with ipilimumab decelerate the tumor growth in the humanized PDX-model Mel9663B and decreased the RNA-expression of PD-1 and PD-L1 in the tumor.

Our humanized mouse models enable a preclinical assessment of immune-based therapeutic antitumor strategies especially when combining the humanized mouse with patient-derived tumor xenografts.

Humanized patient-derived melanoma models

Engraftment and differentiation of hematopoietic cells and detection of human immune cells in the peripheral blood

PD-L1 expression in PDX tumors

Human immune cells in the peripheral blood of humanized mice

Development and characterization of patient-derived melanoma xenograft models

Immune cells markers were used to generate an immunophenotype of PDX.

The calculated immunopnenotypy did not correlate with the load of mutations (number of SNPs).

Growth of human melanomas was confirmed on all humanized mice without evidence for rejection.

Humanized mice received patient-derived melanoma (Mel10936) fragments s.c. Group C was treated with Ipilimumab weekly from day 21 on.

Treatment with ipilimumab induced a minor tumor growth delay.

Nivolumab reduced the tumor growth and in combination with ipilimumab significantly compared to untreated humanized Mice.

An increase of human T cells in the blood was observed after tumor inoculation (data not shown).

In contrast to the Mel1956 model, transplantation of Mel8988 melanoma resulted in a decrease of human T cells in the blood (data not shown).

Ipilimumab treatment increased the number of T cells in the blood and resulted in an accumulation of human leukocytes and T cells in the tumor, however obviously without relevant T-cell activation.

Ipilimumab treatment induced a minor tumor growth delay.

Nivolumab reduced the tumor growth and in combination with ipilimumab significantly compared to untreated humanized Mice.

The combination (ipilimumab+Nivolumab) resulted in an high RNA-expression of CD3, CD8, PD-1 and PD-L1 in treated tumor.

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