Chemokines as tools and targets of personalized cancer immunotherapy

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Adoptive T-cell therapy with chimeric antigen receptor (CAR)-transduced T-cells has achieved impressive benefits for some hematological malignancies: It is approved in the US and in Europe for the treatment of specific forms of rare therapy-refractory leukemias and lymphomas. These approved treatment regimens are derived from autologous patient T-cells, i.e. they represent personalized treatments in its very essence. World-wide, efforts are under way to extend the beneficial effects of CAR-T-cell therapy from hematological malignancies also to solid tumors. However, these endeavors have met with limited success. The two main reasons for this are a) the limited access of adoptively transferred T-cells to the solid tumor; and b) the immunosuppressive microenvironment in the solid tumors.

One strategy to improve the access of adoptively transferred T-cells to the tumor is to engineer these autologous patient-derived T-cells not only with a tumor antigen recognizing receptor (CAR) but also with membrane proteins that promote trafficking of T-cells into the tumor (reviewed in Zhang, Endres and Kobold. Enhancing T cell infiltration to enable cancer immunotherapy. *Immunotherapy* 2019). Attractive candidates for such a “guiding receptor” are chemokine receptors that redirect T-cells to the tumor tissue via a chemokine ligand gradient. To this end, a chemokine receptor is chosen for T-cell transduction, for which the respective ligands are known to be expressed in the tumor tissue.

We have previously shown that engineering T-cells with the chemokine receptor CCR4 (which is bound by the chemokine ligand CCL22, expressed in some tumor tissues) and transferring these cells into tumor-bearing mice, leads to a reduction of tumor growth, presumably by enhanced T-cell infiltration into the tumor (Rapp et al. *Oncoimmunology* 2015). More recently we identified the chemokine receptor CCR6 as an attractive candidate for improving engineered T cell tumor infiltration and anti-tumor efficacy (Lesch et al. Arming T cells with C-X-C-motive receptor 6 enables adoptive T cell therapy of pancreatic cancer. *Eur J Cancer* 2019, abstract). The ligand for CCR6 – CXCL16 – is expressed in several tumor tissues, including pancreatic cancer, both in murine models and in humans.

As an outlook one may envisage that adoptive T-cell therapy will be personalized not only based on the (autologous) source of T-cells but also by the pattern of transduced proteins such
as chemokine receptors. This pattern could be tailored not only to the specific tumor entity but also to the distinct chemokine ligand pattern identified in the tumor of the individual patient.

Chemokines may not only form tools for tumor immunotherapy but also targets. We have shown that the chemokine CCL22 promotes the interaction of regulatory T-cells with dendritic cells in the lymph node (Rapp et al. *J Exp Med* 2019). Blocking this interaction, as shown in CCL22-deficient mice, counter-acts the immunosuppressive actions of T-cells, leading to an improved tumor rejection. Thus, blocking CCL22 e.g. by an anti-CCL22 antibody may form an attractive strategy to mold the immunosuppressive microenvironment and to improve tumor immunotherapy.