

P06.06 **ADOPTIVE CELL THERAPY OF TRIPLE NEGATIVE BREAST CANCER WITH REDIRECTED CYTOKINE-INDUCED KILLER CELLS**

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Background Cytokine-Induced Killer (CIK) cells share several functional and phenotypical properties of both T and natural killer (NK) cells, and represent an attractive approach for cell-based immunotherapy as they do not require antigen-specific priming for tumor cell recognition, and can be efficiently and rapidly expanded *in vitro*. We recently reported that CIK cells have a relevant expression of FcγRIIIa (CD16a), which can be exploited in combination with clinical-grade monoclonal antibodies (mAbs) to redirect their lytic activity in an antigen-specific manner. Here, we report the assessment and the efficacy of this combined approach against triple negative breast cancer (TNBC), an aggressive tumor that still requires reliable therapeutic options.

Materials and methods Different primitive and metastatic TNBC cancer mouse models were established in NSG mice, either by implanting patient-derived TNBC samples or MDA-MB-231 cells subcutaneously or orthotopically into the mammary fat pad, or by injecting MDA-MB-231 cells intravenously. The combined treatment consisted in the repeated intratumoral or intravenous injection of CIK cells and cetuximab, while the mAb alone or CIK cells plus Rituximab served as control treatments. Tumor growth and metastasis were monitored by bioluminescence or immunohistochemistry, and survival was recorded.

Results CIK cells plus cetuximab significantly restrained primitive tumor growth in mice, either implanted with TNBC patient-derived tumor xenografts or injected with MDA-MB-231 TNBC cell line. Moreover, in both experimental and spontaneous metastatic models the combined approach almost completely abolished metastasis spreading and dramatically improved survival. The antigen-specific mAb favored tumor and metastasis tissue infiltration by CIK cells, and in particular led to an enrichment of the CD16a⁺ subset.

Conclusions Data highlight the potentiality of a novel immunotherapy approach where a non-specific cytotoxic cell population can be converted into tumor-specific effectors with clinical-grade antibodies, thus providing not only a therapeutic option for TNBC but also a valid alternative to more complex approaches based on chimeric antigen receptor-engineered cells.

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P06.07 **CXCR6 EXPRESSION ENHANCES ACCUMULATION OF ANTI-MESOTHELIN CAR T CELLS AT THE TUMOR SITE AND THEIR THERAPEUTIC EFFICACY IN PANCREATIC CANCER XENOGRAPTS**

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Background Chimeric antigen receptor (CAR) T cell therapy is currently approved for the treatment of some hematological malignancies. However, CAR T cells have so far lacked efficacy in the treatment of solid tumors. A major hurdle of CAR T cell therapy is the limited infiltration of CAR T cells into tumor tissue. Chemokine receptors enable immune cells to migrate along a chemokine gradient. Here, we show that overexpression of the C-X-C chemokine receptor 6 (CXCR6) enhances CAR T cell accumulation in C-X-C motif ligand 16 (CXCL16)-positive xenograft pancreatic cancer models, resulting in increased anti-tumor potency of anti-mesothelin CAR T cells. **Materials and Methods** Human T cells were retrovirally transduced with an anti-mesothelin CAR and CXCR6. NSG mice were injected subcutaneously with mesothelin-CXCL16-overexpressing tumor cells. Mice were treated once with CAR-, CAR-CXCR6- or mock-transduced T cells when tumors were palpable and tumor size was monitored with a caliper. In a separate tracking experiment, subcutaneous tumors were established as described above and the presence of T cells at the tumor site was determined by FACS analysis within one week after adoptive T cell transfer. For orthotopic xenograft experiments mesothelin-CXCL16-overexpressing tumor cells were directly injected into the pancreas of NSG mice and one-time treatment with CAR-, CAR-CXCR6- or mock T cells was performed 5 days post tumor injection.

Results In a subcutaneous xenograft model of pancreatic cancer CXCR6-expressing CAR T cells displayed improved anti-tumoral potency compared to CAR T cells without CXCR6, resulting in prolonged survival of mice and tumor clearance in 9 out of 10 CAR-CXCR6-treated mice. A tracking experiment confirmed the increased accumulation of CAR-CXCR6 T cells compared to CAR T cells at the subcutaneous tumor site, suggesting increased migratory capacity of CAR-CXCR6-transduced T cells towards CXCL16-expressing tumors as the mode of action. Treatment of orthotopic pancreatic cancer xenografts similarly revealed prolonged survival of CAR-CXCR6-treated animals in comparison to CAR-treated animals, suggesting improved anti-tumor efficacy of CAR-CXCR6-transduced T cells.

Conclusions Forced expression of CXCR6 in anti-mesothelin CAR T cells increased the accumulation of CAR T cells at the CXCL16-positive tumor site, resulting in improved survival of treated mice and in complete tumor rejection in the majority of cases. This data reveals the potential of CXCR6 to direct CAR T cells to the tumor site and this approach may therefore be an attractive strategy to target a major pitfall in the translation of CAR T cell therapy to solid tumors.

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P06.08 **IMMUNOMODULATORY BIOMARKERS IN NEOADJUVANT CHEMOTHERAPY OF BREAST CANCER**

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Background Neoadjuvant chemotherapy (NAC) with epirubicin/cyclophosphamid followed by docetaxel (E/C->D) is