

Conclusions In sum, we have established a new model suitable for intravital imaging that will help identify limitations of CAR-T cells activity in the context of a solid tumor.

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P09.07 DETERMINING POTENCY, ACTIVATION AND EXPANSION OF ANTIGEN SPECIFIC T CELLS

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Background CAR/T Cell therapy relies on Cells with engineered receptors that bind tumour cells, then transduces a stimulatory signal meant to activate the engineered Cell to kill the tumour cell. Clinical experience has indicated that activating T-cells through its TCR alone isn't going to be sufficient to mount and maintain an effective anti-tumour response. Adding additional strength to the T cells by providing a 2nd or 3rd engineered co-stimulatory signal are currently pursued strategies within Cell therapy. In vitro assays are needed to evaluate the effect of the added co-stimulatory signals and to evaluate the potency of engineered T cells. Most current assays are based on cell-cell interaction which makes them hard to standardize. We have explored Dextramer technology as an artificial antigen-presenting scaffolds able to stimulate and activate specific T cells. Dextramer displaying MHCp complexes and anti-CD28 antibody (MHC/a-CD28 Dextramer) were used to stimulate PBMCs or a TCR engineered T cell line.

Materials and Methods Healthy donor PBMCs comprising virus-specific CD8+ T cells or TCR engineered T cell lines were incubated with MHC/a-CD28 Dextramer in culture medium for 6 hours to 14 days. Antigen specific T cells were following analyzed for i) activation by upregulation of CD69 and CD137, ii) cytokine production (IFN-gamma, TNF-alpha) and iii) proliferation.

Results MHC/a-CD28 Dextramer could stimulate an activate specific T cells in PBMC sample: i) an upregulation of early activation markers, CD69 and CD137 was observed, ii) increase in cytokine production, INF-gamma and TNF-alpha could be measured intracellular, and iii) a 15 fold expansion of T cells specific for the MHCp complex of the Dextramer was measured, all proliferating cells were expressing Ki-67. No stimulation or activation of T cells were observed when incubating cell samples with MHC/a-CD28 Dextramer displaying negative control MHCp. Similar results were obtained when stimulating engineered T cell line.

Conclusions We have shown a simple technology to explore effect of engineered co-stimulatory signals, and evaluate potency of engineered T cells. MHC/a-CD28 Dextramer were able to stimulate, activate and expand specific T cells. The activation was highly antigen (i.e. MHCp) specific and CD28 co-immobilization dependent.

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10. Cell therapy in haematologic diseases

P10.01 NUTRITIONAL AND IMMUNOMETABOLIC MEASURES FOR RISK ASSESSMENT IN ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Background The hematopoietic transplant comorbidity index (HTC-CI) has been developed to determine treatment-related morbidity following allogeneic hematopoietic stem cell transplantation (alloHSCT) and includes obesity and diabetes as risk factors. On the other hand, chronic low-grade inflammation which is regularly associated with obesity and represents a mechanism of insulin resistance might mediate beneficial immune effects as demonstrated in the context of immune-check point inhibition cancer treatment. Literature on the role of a high body mass index (BMI) prior to alloHSCT remains controversial likely due to the complexity of the involved mechanisms that also comprise of increased catabolic rates and the immunonutritional status. In this study, we evaluated clinical outcomes in a large cohort of consecutive patients who underwent alloHSCT. Specifically, we analyzed pre-transplant BMI and immunonutritional scores as well as their dynamic changes in the early post-transplant phase with regard to survival and toxicities.

Materials and Methods Clinical records of 664 consecutive patients undergoing alloHSCT between 2012 and 2017 at the Department of Medicine I, University Hospital of Cologne, Germany, were retrospectively analyzed. Patients were categorized into four BMI classes and three immunometabolic risk groups according to the modified Glasgow Prognostic Score (mGPS) measured pre-transplant and on day 30 post-transplant. Overall survival (OS), non-relapse mortality (NRM) and the development of a clinically relevant acute graft-versus-host disease (GvHD) ≥ 2 grade were compared using Kaplan-Meier survival analysis. Additional analyses stratified for sex and focused on a disease and transplant setting homogenized cohort.

Results Median BMI of the cohort was 24.6 (15.1-50.4) kg/m². OS and NRM differed significantly between BMI classes (OS p = 0.02; NRM p = 0.05), with a significant survival benefit of overweight (median OS: 21 and 22 months in normal weight and obese, > 50% alive after 60 months in overweight). In contrast to the male cohort, in females also obesity had a favourable impact (p = 0.50; median OS: 16 months in normal weight; 35 months in overweight and >50% alive after 60 months in obese). mGPS classes, both determined pre-transplant and on day 30, experienced significantly different OS and NRM (OS p < 0.001; NRM p < 0.002), in which hypoalbuminemia combined with elevated C-reactive protein (mGPS 2) correlated with worst OS, NRM and a tendency of higher GvHD incidence. The extend of mGPS increase from day 0 to 30 impacted all outcomes significantly (OS p = 0.02; NRM p = 0.05; GvHD p = 0.01).

Especially an increase to an mGPS of 2 was associated with significantly worse OS, NRM and higher GvHD incidence (median OS: 13 and 7 months in mGPS 0->2 and 1->2, respectively; 49 months in mGPS 0->1).

Conclusions Our data suggest a more complex role of metabolic pathologies as currently reflected by obesity and diabetes categories within the HTC-CI. Therefore, future prospective studies that include body composition as well as sensitive measures of disturbed glucose tolerance and metabolic rates are warranted to determine immunometabolic risk factors for alloHSCT outcomes.

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11. Combination Therapy

P11.01 ONCOLOGICAL OUTCOMES OF LAPAROSCOPIC VERSUS OPEN RADICAL TOTAL GASTRECTOMY FOR UPPER-MIDDLE GASTRIC CANCER AFTER NEOADJUVANT CHEMOTHERAPY

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Background Laparoscopic technique has been increasingly used in gastrectomy, but the safety and feasibility of the laparoscopic total gastrectomy (LTG) for advanced proximal gastric cancer (PGC) after neoadjuvant chemotherapy (NAC) is unclear.

Materials and Methods A retrospective analysis of 146 patients who received NAC followed by radical total gastrectomy at Fujian Medical University Union Hospital from January 2008 to December 2018 was performed. The primary endpoints were long-term outcomes.

Results The patients were divided into two groups: 89 were in the LTG group and 57 were in the open total gastrectomy (OTG) group. The LTG group had a significantly shorter operative time (median 173 min vs. 215 min, $p < 0.001$), less intraoperative bleeding (62 ml vs. 135 ml, $p < 0.001$), higher total lymph-node (LN) dissections (36 vs 31, $p=0.043$), and higher total chemotherapy cycle completion rate (≥ 8 cycles) (37.1% vs. 19.7%, $p = 0.027$) than OTG. The 3-year overall survival (OS) of the LTG group was significantly higher than that of the OTG group (60.7% vs. 35%, $p = 0.0013$). Survival with inverse probability weighting (IPW) correction for Lauren type, ypTNM stage, NAC schemes and the times at which the surgery was performed showed that there was no significant difference in OS between the two groups ($p = 0.463$). Postoperative complications (25.8% vs. 33.3%, $p = 0.215$) and recurrence-free survival (RFS) ($p = 0.561$) between the LTG and OTG groups were also comparable.

Conclusions In experienced gastric cancer surgery centers, LTG is recommended as the preferred option for such patients who performed NAC, owing to its long-term survival is not inferior to OTG, and it offers less intraoperative bleeding, better chemotherapy tolerance than conventional open surgery.

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P11.02 A COMPLEX HUMAN TUMOR ORGANOID MODEL CONSISTING OF MALIGNANT CELLS, FIBROBLASTS AND IMMUNE CELLS ENLIGHTS THE EFFECT OF CHEMOTHERAPY-INDUCED SENESCENT TUMOR CELLS ON NK-CELL ANTI-TUMOR RESPONSES

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Background Primary human organoids have been shown to be predictive for selective chemotherapy and thus be a valuable model for cancer research. One of many tumor evasion strategies in response to DNA-damaging chemotherapy treatment is the induction of senescence to acquire a state of resistance. Fortunately, natural killer (NK) cells recognize senescent tumor cells, get activated and trigger tumor killing in assistance of T-cells, as it was shown in mice studies and cell lines. Additionally, it has been described that activation of the STING pathway strongly enhance NK-cell responses. Therefore, we hypothesized, that STING-activated NK-cells are superior in killing chemotherapy-induced senescent tumor organoids. To test this hypothesis in a primary human disease-relevant model, we established a complex system consisting of tumor organoids, matched primary cancer-associated fibroblasts (CAFs) and immune cells.

Materials and Methods To establish complex organoid cultures, we investigated various air-liquid-interface (ALI) culture conditions of primary tumour spheroids, CAFs and peripheral blood mononuclear cells (PBMCs). Senescence was induced by Etoposide treatment and was verified by β -galactosidase staining. Immune cells were activated by either ionomycin and PMA, or a STING agonist ADU-S100.

Results Immune cell viability was preserved for 48 hours in the established ALI culture consisting of PBMCs and organoids in one phase and fibroblasts in a second compartment. Functional applicability of the system was evaluated through ionomycin and PMA induced immune cell activation which resulted in tumor cell death as quantified by zombie violet positive staining. Confocal microscopy further verified immune cell infiltration and immune cell mediated disintegration of organoids. Senescence was inducible by DNA-damaging chemotherapy in 3D co-culture of tumor organoids and CAFs. Moreover, a combination of senescence induction by DNA-damaging chemotherapy and subsequent STING-pathway activation led to a more pronounced NK-cell activation (CD69) and degranulation (CD107a) in contrast to non-senescent controls.

Conclusions We developed a complex 3D culture system of tumor, stromal and immune cells to mimic the tumor micro-environment and to assess the impact of senescent organoids on STING-activated immune cells in a primary human model.

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