Oral Presentations

10 Young researcher session

10.01 EFFECTIVE SOLID TUMOR THERAPY THROUGH ENHANCED RECRUITMENT AND IMMUNE SUPPRESSION SHIELDED T CELLS

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Background CAR T cell therapy remains ineffective in solid tumors. Scarce T cell infiltration and T cell suppression at the tumor site are two notable therapy limitations. T regulatory (Treg) cells are capable of suppressing effective anti-tumor responses through inhibitory factors such as transforming growth factor β (TGF- β). Treg cells expressing the C-C chemokine receptor 8 (CCR8) have been found to accumulate and to correlate with poor prognosis in breast cancer. We postulated that CCR8 could be exploited to redirect effector T cells to the tumor site while a dominant-negative TGF- β receptor 2 (DNR) can simultaneously shield them from TGF- β .

Materials and Methods CCR8 and DNR can be expressed in murine and human T cells upon retroviral transduction. T cell receptor (TCR) and chimeric antigen receptor (CAR) antigen specific models in murine and human systems were utilized. qPCR, IF microscopy, ELISA and the cancer genome atlas (TCGA) database were used in the steps of ligand identification and hypothesis generation. We employed flow cytometry and multi-photon intra-vital microscopy to interrogate infiltration, proliferation and phenotype of T cell products. Mechanistically, CRISPR was used to dissect the role of the CCL1-CCR8 positive feedback loop in T cell therapy.

Results We identified that in an in vivo pancreatic murine model of cancer, the CCR8 gene was upregulated in tumor infiltrated lymphocytes compared to T cells that accumulated in the spleen. In this same tumor model, CCL1 could be detected in tumor explants. We identified that this secreted CCL1 from activated effector T cells potentiates a feedback loop for CCR8⁺ T cell recruitment to the tumor site. The introduction of CCR8 and DNR receptors in primary T cells improved migration towards CCL1 and improved proliferation capacity in the presence of TGF- β . Besides these effects, these receptors did not further impact effector and memory phenotype or secretome of T cell products. The CCR8-driven sustained and improved infiltration synergized with TGF- β -shielding conferred by the DNR for improved therapeutic efficacy, allowing tumor rejection in models that are otherwise completely resistant to CAR T cell therapy.

Conclusions We conclude that the combination of CCR8- and DNR-transduction into antigen-specific T cells can exploit two critical biological axes to render T cell therapy effective in solid tumors such as pancreatic cancer. Beyond TGF- β , relieving other immunosuppressive axes may further sustain a CCL1 feedback loop mechanism to improve anti-tumoral

function of CCR8+ ACT. This therapeutic approach could be extended to other Treg-rich solid tumor entities where limited infiltration into the tumor and intra-tumoral T cell proliferation prevent therapeutic success. Furthermore, the CCL1-CCR8 axis heralds the potential to be used as a target to improve the efficacy of immunotherapies beyond ACT.

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10.02 GENOMIC HLA HOMOZYGOSITY IS FREQUENT IN ESOPHAGEAL ADENOCARCINOMA AND RELATED TO LOW IMMUNOGENICITY

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Background Classical human leukocyte antigen (HLA) class I molecules are expressed by most somatic cells and present peptides to cytotoxic T cells. The HLA-genotype of an individual contains up to six different HLA-I molecules and defines the repertoire of peptides that can be presented to cytotoxic T cells. Homozygosity for one or more HLA-loci could translate in a smaller repertoire of tumour neoantigens possibly presented to cytotoxic T cells in an individual and potentially predispose such individuals with a disadvantage to fight a nascent tumour.

Material and Methods High-resolution HLA-genotyping from germline normal DNA of 80 esophago-gastric adenocarcinoma (EGA) patients was performed with the NGS method by Illumina. Whole exome sequencing (WES) was performed on tumor tissue and normal peripheral blood cells (n=39). The data were processed, and non-synonymous mutations were called. The amount of potential high-affinity binders derived from 10 cancer testis antigens (CTAs) frequently expressed in EGA and non-synonymous mutations obtained from WES data were determined using an in-silico approach for MHC-binding (IEDB.org). RNA-extraction and gene expression profiling were performed using the NanoString technology.

Results We compared the frequency of HLA homozygosity in EGA patients to an HLA-matched reference population derived from a large cohort of bone marrow donors (n=7.615 out of 615.017 donors). We demonstrate that EGA patients are more likely to be homozygous for at least one HLA-I gene than the control population. In EGA patients, 35% of HLA-A, -B, and -C alleles were homozygous in comparison with 19% of HLA alleles among the HLA-matched general population. This difference corresponded to an odds ratio (OR) for homozygosity of 2.282 (95% confidence interval (CI) 1.442-3.615, p<0.001). The odds ratios for homozygosity at HLA-A (OR=1.885, CI=1.111-3.236, p<0.05), HLA-B (OR=3.045, CI=1.346-6.499, p<0.05) and HLA-C (OR=2.170, CI=1.445-3.579, p<0.05) were significantly different. We then aimed to estimate the influence of HLA-homozygosity in the context of tumour immune surveillance. Predictions by IEDB analysis resource tool indeed showed a reduced repertoire of high and moderate-affinity MHC-