INTERLEUKIN-22 REGULATES ANTI-TUMOR IMMUNITY
IN MOUSE MODELS OF LUNG AND BREAST CARCINOMA

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Background High expression of CD155 (poliovirus receptor, PVR) is associated with a poor prognosis of lung adenocarcinoma (LUAD) and triple-negative breast cancer (TNBC) patients. When overexpressed, this molecule inhibits the antitumor function of NK and cytotoxic T cells through binding to its inhibitory co-receptors TIGIT and CD96, and downregulates the stimulatory CD226 (DNAM-1). However, the exact mechanism of CD155 overexpression on the tumor cells and, therefore, promotes tumor function of NK and cytotoxic T cells through binding to its inhibitory co-receptors TIGIT and CD96, and downregulates the stimulatory CD226 (DNAM-1). However, the exact mechanism of CD155 overexpression on the tumor cells and, therefore, promotes tumor function of NK and cytotoxic T cells. Moreover, this effect is reversed when CD155 is expressed on the tumor cells independent of its natural regulation, which enables lung metastases in IL-22 deficient animals. Phenotypically, NK cells in IL-22 knockout mice have a higher expression of co-stimulatory receptor CD226, which is linked to the antitumor potential of these cells.

Conclusions Here we demonstrate a novel pathway of cytokine-mediated cancer progression, where IL-22 is capable of inducing CD155 on the tumor cells and, therefore, promotes an immunosuppressive tumor microenvironment. This highlights the potential of IL-22 as a target for immunotherapy considering the complexity of the CD155-dependent immunoregulatory network.

Conclusions With this set of 7 novel CT-specific TCRs we expand the arsenal of tumor specific TCRs. With this expanding library of TCRs it would be possible to select in future for each cancer patient, based on HLA typing and gene expression, a useful TCR to generate a personalized TCR-gene therapy products. In addition, patients could be treated with multiple TCRs to enhance the efficacy and increase the durability of clinical responses by reducing the likelihood of tumor escape.


Poster Presentations

P01 Emerging concepts/new agents

P01.01 SAFETY AND EFFICACY STUDY OF PEMBROLIZUMAB IN COMBINATION WITH LENVATINIB IN PARTICIPANTS WITH HEPATOCELLULAR CARCINOMA (HCC) BEFORE LIVER TRANSPLANT AS NEOADJUVANT THERAPY—PLENTY RANDOMIZED CLINICAL TRIAL

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Background Patients with hepatocellular carcinoma (HCC) who exceed standard Milan criteria suffered from high post-transplant recurrence rate. This study will evaluate the safety and efficacy of pembrolizumab in combination with lenvatinib as neoadjuvant therapy in participants with HCC exceeding Milan criteria before liver transplant.

Materials and Methods Participates would be randomly assigned (1:1) to experimental or Comparator/Control by computer-generated allocation based on the envelope method and the hierarchical block randomization method (hierarchy: BCLC stage and AFP level). The envelopes are sealed opaque, and sequentially numbered. Randomization is performed by the trial coordinator. The random number table and the block assignment number table will be kept confidential by the full-time secretary of this project. Center-stratified block-permutated randomization is used in this trial. Then permuted block randomization is used for each stratum with a block size of 4.

Results The initial first patient was recruited in August 2020.

References


P01.02 TLR-MEDIATED SUPPRESSION OF THE CCL22-CCR4 AXIS AS A NEW TARGET FOR TUMOR IMMUNOTHERAPY

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Background Unmethylated CpG-DNA is a potent ligand for the endosomal Toll-like receptor-9, important for the immune activation to pathogen-associated molecules.1 CpG and other TLR-ligands show effective immunotherapeutic capacities in cancer treatment by inducing an antitumorigenic immunity.2 They are able to reduce tumor progression by induction of intratumoral secretion of the immunoregulating chemokine CCL223 and subsequent recruitment of immunosuppressive regulatory T cells (Treg), which express CCR4 the only so far known receptor for CCL22.4 Our recent work has shown that CCL22 secretion by dendritic cells (DC) in the lymph node, mediates tolerance by inducing DC-Treg contacts.5 Indeed, in the absence of CCL22, immune responses to vaccination were stronger and resulted in tumor rejection.6 Therefore, we are aiming to investigate the effects of TLR-ligands on systemic CCL22 levels, elucidating all involved mechanisms to identify new targets for cancer immunotherapy.

Materials and Methods T, B and CD11c+ DCs of wildtype (wt) and RAG1−/− mice were isolated from splenocytes by magnetic-activated cell sorting for in vitro assays. Different co-cultures were incubated with CpG and GM-CSF, known as an CCL22 inducer.7 For in vivo experiments, wt mice were treated with CpG, R484 or poly(I:C) alone and in combination with GM-CSF. CCL22-levels in a number of organs were analyzed.

Results Analyzing the different immune cell compartments in vivo, we found that DCs in whole splenocytes secrete CCL22 during culture while DC cultured alone showed no CCL22 secretion. When treated with CpG, CCL22-levels were reduced in splenocytes, while it was induced in DC culture alone. The same results were seen when RAG splenocytes, that lack functional B and T cells, were cultured with CpG. CpG treated B cells were able to suppress CCL22 secretion by DC unlike T cells alone. Co-cultures of T and B cells treated with CpG, however, induced the strongest CCL22 suppression in DC. In vivo, we could show that all TLR ligands treated reduced CCL22 in a number of organs significantly. Furthermore, CpG showed the strongest suppression of CCL22 even in the presence of the CCL22 inducer GM-CSF.5

Conclusions We could show that B cells with T cells mediate CCL22 suppression by TLR ligands. The fact that CpG was able to reduce CCL22 levels even in the presence of the inducer GM-CSF demonstrates the potent CCL22 suppressive capacity of TLR ligands.