

binders (both CTA-derived and mutation-derived peptides) in the homozygous cohort. Our findings demonstrate a reduced amount of potentially immunogenic peptides in EGA patients with HLA-homozygosity for at least one locus, which may result in impaired cancer immunosurveillance. In line with this observation, we also found increased levels of CTA expression in homozygous compared to heterozygous patients. After artificial modification of the genotype of homozygous patients to a heterozygous genotype, the set of predicted good-binding peptides was comparable to the heterozygous cohort.

Conclusion Our results highlight the effect of HLA-I homozygosity on the immunopeptidome as important prerequisite of anti-tumor immunity. The high frequency of genomic HLA-I homozygosity observed in the EGA cohort may reflect an increased cancer risk for these patients. Together with previous reports demonstrating reduced survival after checkpoint therapy, our study suggests consideration of germ-line HLA-homozygosity for the design and interpretation of immunotherapeutic trials.

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10.03 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 anti-tumor function of NK and cytotoxic T cells through binding to its inhibitory co-receptors TIGIT and CD96, and downregulation of stimulatory CD226 (DNAM-1). However, the exact mechanism of CD155 overexpression on the tumor cells remains unclear. Here we demonstrate that interleukin-22 (IL-22), a cytokine known to promote cancer progression, induces upregulation of CD155 on tumor cells in mouse models of breast and lung cancer and may, thus, inhibit antitumor immunity and promote lung metastasis.

Materials and Methods To study the influence of IL-22 on antitumor immunity, we utilize IL-22-deficient animals in syngeneic mouse models of metastatic breast and lung cancer. For this purpose, we generated tumor cells deficient in IL-22

receptor (IL-22R) or in CD155 and tumor cells, that constantly express CD155 independent of its natural regulation. Here, we determine the incidence of metastasis and antitumor NK and T cell responses in the lung, the primary site of metastasis.

Results We demonstrate that murine cancer cells upregulate CD155 surface expression upon treatment with recombinant IL-22, whereas this effect is abolished in the absence of IL-22R. Furthermore, IL-22-deficient animals have a lower metastatic burden in the lung and demonstrate a dramatic increase in IFN- γ production in NK, and, to a lower extent, 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.

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10.04 A LIBRARY OF NOVEL CANCER TESTIS SPECIFIC T-CELL RECEPTORS FOR T-CELL RECEPTOR GENE THERAPY

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Background The positive clinical effect of T-cell receptor (TCR) gene therapy on tumor regression has previously been demonstrated by NY-ESO-1 TCR-gene therapy. To seriously increase the number of cancer patients that can be treated with TCR-gene therapy we aim to identify a novel set of high-affinity Cancer Testis (CT) specific TCRs targeting different CT-antigens in a variety of prevalent HLA-class I alleles.

Materials and Methods In this study, we selected by bioinformatic tools the most promising CT-genes to target, and from these genes we identified by HLA-peptidomics the naturally processed and presented HLA-class I peptides. With these peptides HLA-tetramers were generated, and by MACS enrichment and single cell sorting CT-specific CD8⁺ T-cell clones were selected from the allo-HLA repertoire of healthy donors. By performing several different functional assays the high function avidity CT-clones with a safe recognition pattern were selected. To evaluate the potential for clinical application in TCR-gene therapy, TCRs were sequenced, and transferred into peripheral blood derived CD8⁺ T cells.

Results In total we identified, 7 novel CT-specific TCRs that effectively target MAGE-A1, MAGE-A3, MAGE-A6 and MAGE-A9 expressing tumor cells in the context of HLA-A1, -A2, -A3, -B7, -C7 and -B35.