RIG-I ACTIVATION ENHANCES MELANOMA IMMUNOCENNIGICITY AND IMPROVES ANTI-TUMOR T CELL RESPONSES IN COMBINATION WITH ANTI-PD-1 IMMUNE CHECKPOINT BLOCKING ANTIBODIES

Background Clinical efficacy of immune checkpoint blocking (ICB) therapy critically relies on the killing of melanoma cells by CD8+ T cells, becoming activated upon recognition of tumor antigens presented by HLA class I (HLA-I) surface molecules. Patient-derived melanoma cells can escape from cytotoxic T cell effector functions by loss of HLA-I surface expression due to the silencing of HLA-I antigen processing and presentation machinery (APM) genes.

Material and Methods Seeking for a strategy to restore HLA-I expression, we transfected melanoma cells obtained from distinct patient metastasis with synthetic short double stranded RNA (3pRNA), an activating ligand of the cytosolic innate pattern recognition receptor RIG-I. 3pRNA-transfected melanoma cells were analyzed for HLA-I surface expression by FACS analysis and gene expression of HLA-I APM components by qPCR. In vivo 3pRNA-transfected tumors were analyzed for HLA-I expression by immunohistochemistry staining. Furthermore, T cell activation after coincubation with 3pRNA-transfected melanoma cells was determined by IFNγ-ELISPOT assay. The effect of combined 3pRNA and blocking anti-PD-1 antibody treatment on T cell activation was measured by intracellular cytokine staining and FACS analysis.

Results Activation of RIG-I by 3pRNA increased the expression of HLA-I APM components and strongly enhanced recognition of melanoma cells by autologous CD8+ T cells. Based on these findings, we asked whether the combination of 3pRNA and blocking anti-PD-1 antibodies could improve antitumor T cell responses in an anti-PD-1 non-responder patient model. Indeed, T cell activation by 3pRNA-transfected melanoma cells was significantly increased in the presence of anti-PD-1 antibodies. In line with the enhancement of antitumor T cell responses, we found an association of elevated RIG-I mRNA levels with prolonged patient survival in TCGA melanoma samples.

Conclusions In summary, this study demonstrates a beneficial effect of RIG-I activation on antigen presentation and T cell recognition of melanoma cells. Improved T cell responses by combined 3pRNA and anti-PD-1 treatment suggests that combinational therapy could be a strategy to overcome T cell resistance in melanoma.


On Demand Talks:

On Demand Talks: Tumor Microenvironment

TUMOR LACTIC ACIDOSIS ALTERS DECISIVE T CELL ACTIVITIES

Background Adoptive T cell therapy is a promising treatment strategy for tumor patients. However, when entering the tumor microenvironment (TME), T cells lose their effector function showing reduced degranulation and cytokine secretion. Besides T cell inhibition through checkpoint pathways (i.e. PD-1/L1, CTLA-4), suppressor cells (i.e. TAM, Treg) and cytokines (i.e. IL-10, TGF, VEGF), various metabolites of the TME also counteract antitumoral activities. Among the latter, lactate and extracellular acidosis are byproducts of the cancer metabolism and commonly observed in high concentrations in...
T cell therapies for cancer treatment are challenging to develop because of the complex mechanisms and cell interactions that underly T cell-mediated tumor killing. Current technologies rely on correlating phenotype, function, and gene expression based on experiments performed on different populations of T cells because no one platform is able to assess cell surface marker expression, cytokine secretion, and tumor cell killing activity of the same T cell and recover this cell for downstream genomic analysis. Here we share two use cases - CART cell functional screening and TCR sequence recovery following functional assay - that demonstrate how the T Cell Analysis Suite on the LightningTM optofluidic platform can be used to directly link T cell phenotype and function (IFNγ secretion and tumor cell killing) to genotype (TCR sequence recovery) at a single-cell level and on the same T cell, enabling deeper and more thorough characterization of how T cells mediate tumor cell death and potentially the development of more efficacious therapies.

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