1128 NEW VIRAL-DELIVERY OF GLYCAN-MODIFYING SIALIDASE INDUCES ANTI-TUMOR IMMUNITY

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Background Recent advancements in the stimulation of the immune microenvironment and anticancer immune responses with immune checkpoint inhibitors (ICI) has improved the outcome of cancer patients. However, primary and acquired resistance significantly diminish the success of ICI and only a minority of patients benefit. Thus, new strategies are urgently needed in order to induce long-term remissions with cancer immunotherapy. Changes of glycosylation have a significant impact on cancer biology and cancer progression. New therapies that aim to remodel the tumor glycosylation and reactivate the immune system are being explored. In particular, approaches that target the sialoglycan-Siglec glyco-immune checkpoint showed very promising results in pre-clinical animal models and are currently under investigation in early clinical trials.

Methods An adeno-associated virus (AAV) was constructed to express influenza sialidase under a CMV promoter (AAV-sia). Efficacy of sialidase production in transduced cells and the sialidase activity were tested in *in vitro* assays and mouse tumor models after intratumoral injection. In addition, efficacy of immune reactivation against tumors and cancer control was tested in various transplantable, syngeneic mouse models. Immune reactions were further characterized by flow cytometry and single cell RNA sequencing.

Results Upon AAV-sia treatment, cancer cells express sialidase on the cell surface and are able to cleave sialic acid in the tumor microenvironment in mouse models. We are further able to show an inhibitory effect on tumor growth and survival in syngeneic tumor models responsive and unresponsive to PD-1 blockade. Furthermore, a relevant synergism combining AAV-sia and anti-PD-1 treatment was observed. Mechanistic studies demonstrate an increased activation of $CD8^+$ T cells, a polarization of myeloid cells towards a less immune-suppressive phenotype and an increase in conventional dendritic cell infiltration. In addition, scRNAseq data shows an increase in a macrophage population that up-regulate M1-like genes as TNF-alfa, CD80, MHCII, NOS2, IL1-beta and CXCL9. Despite local injection and desialylation, we observed also a growth inhibition on distant tumor sites and an increase in tumor-specific T cells suggesting a systemic immune activation.

Conclusions Taken together, AAV-sia removes the immune-suppressant carbohydrate sialic acid from the tumor microenvironment and cancer cells rendering them more vulnerable for destruction by immune cells.

Ethics Approval All mouse experiments were approved by the local ethics committee (Approval 3036, Basel Stadt, Switzerland) and performed in accordance with the Swiss federal regulations

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