Targeting tumor sialylation in combination with checkpoint inhibitors for cancer immunotherapy

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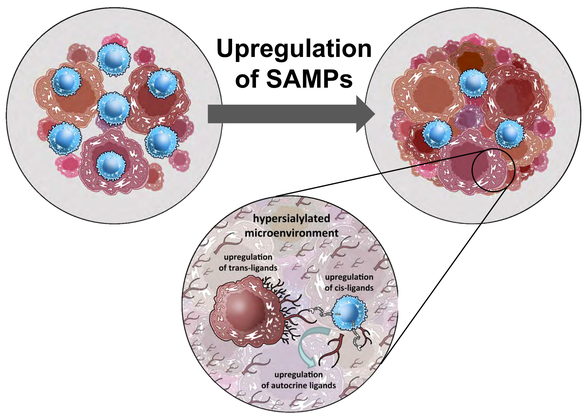
Abstract. **Immunotherapy with immune checkpoint inhibitors (ICI) targeting PD-(L)1 and CTLA-4 has been successfully introduced into routine oncological practice. Despite the success of ICI, most patients derive no benefit from ICI therapy and new approaches are needed including combinations of ICI with new immunotherapeutics. Recent evidence demonstrated that hypersialylation of tumor cells and the extracellular tumor matrix is a targetable pathway of adaptive immune escape in cancer. Our current work shows that targeting hypersialylation in combination with PD-1 or CTLA-4 inhibition induces tumor control in different preclinical mouse models and T cell activation in primary patient tumor samples. While binding of hypersialylated ligands to inhibitory Siglec receptors on tumor-infiltrating immune cells led to an immune-inhibitory microenvironment and T cell inhibition, tumor-targeted desialylation was achieved by antibody-sialidase constructs targeted to human HER2. Targeted desialylation led to intratumoral T cell activation and T cell-dependent tumor rejection, which was non-redundant to PD-1 or CTLA-4 inhibition. The efficacy was dependent on inhibitory Siglecs. Accordingly, ICI therapies in Siglec-deficient animals were more efficient and priming of T cells Siglec-dependent. Finally, desialylation of the primary breast tumors led to T cell activation. Taken together, we demonstrate that systemic targeting of tumor hypersialylation is a new immunotherapeutic modality and can be combined with PD-(L)1 and/or CTLA-4 inhibition for further clinical development.**

The sialoglycan-Siglec immune checkpoint in cancer.

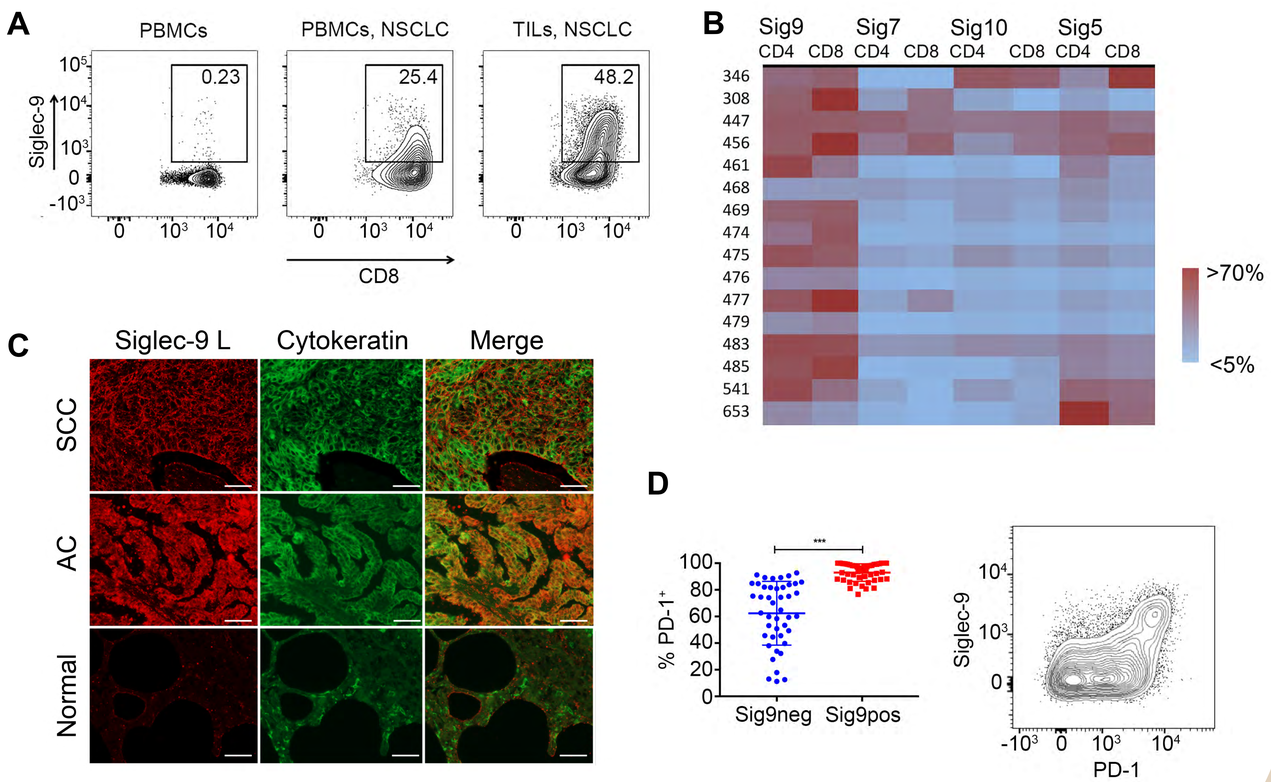


Sialic acid-containing glycans (sialoglycans) are upregulated in many different cancers. Sialoglycans can serve as self-associated molecular patterns (SAMPs) and are detected by Siglec receptors.

Several recent studies have shown that sialoglycans inhibit the immune system in cancer by binding to Siglec receptors on immune cells.

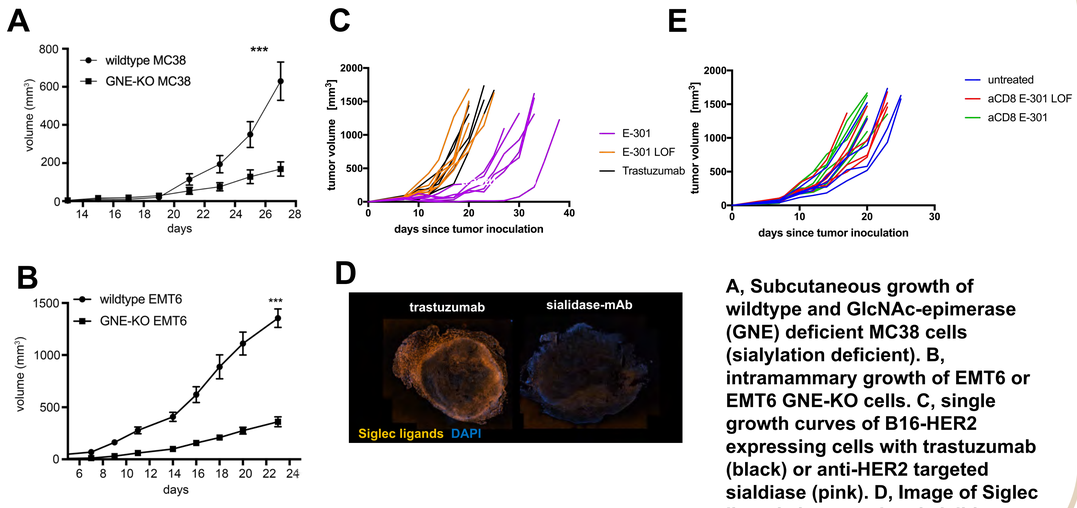
The sialoglycan-Siglec axis can be regarded as a new immune checkpoint in cancer.

Tumor-specific T cells upregulate Siglec-9



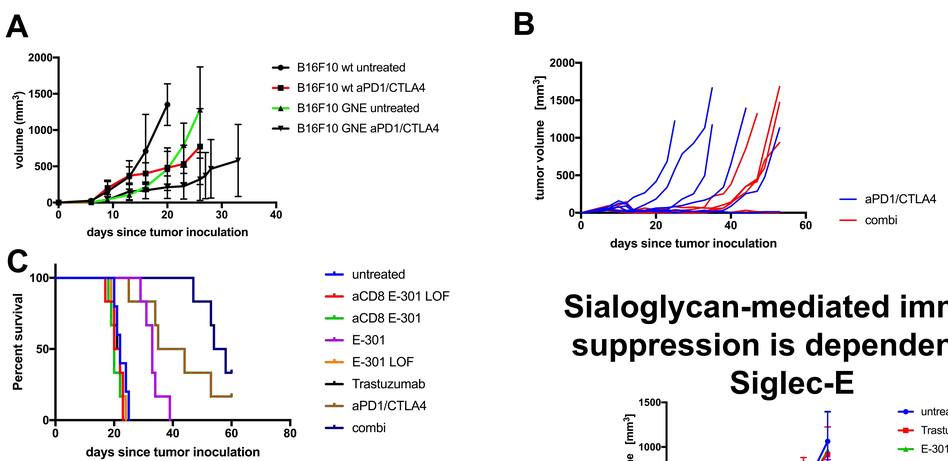
A, T cells in the periphery from healthy donors are compared to PBMCs from NSCLC patients or TILs. B, The heat map shows the expression of different Siglecs on TILs from primary NSCLC samples. C, staining of Siglec-9 ligands was performed in squamous cell carcinoma (SCC) or adenocarcinoma (AC). D, PD-1 expression on TILs from primary NSCLC is shown.

Sialoglycans inhibit anti-tumor immunity.



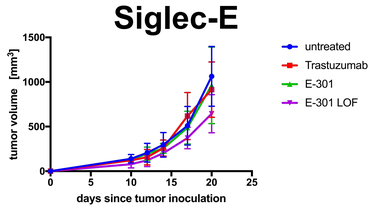
A, Subcutaneous growth of wildtype and GlcNAc-epimerase (GNE) deficient MC38 cells (sialylation deficient). B, intramammary growth of EMT6 or EMT6 GNE-KO cells. C, single growth curves of B16-HER2 expressing cells with trastuzumab (black) or anti-HER2 targeted sialdiase (pink). D, Image of Siglec ligands in control and sialidase treated animals. E, CD8 depletion.

Targeting sialglycans can be combined with PD-1 and CTLA-4 blockade



A, Subcutaneous model of B16 wildtype and GNE-KO cells untreated or treated with anti-PD1/CTLA4 antibodies. B, Growth of B16-HER2 with anti-HER2-sialidase (E-301) and anti-PD1/CTLA4 (combi) or ICI alone. C, Survival of mice with B16-HER2 tumors and different treatment conditions (CD8 depletion, Loss Of Function (LOF) sialidase-Ab construct).

Sialoglycan-mediated immune suppression is dependent on Siglec-E



B16-HER2 in Siglec-E deficient mice treated with trastuzumab, sialidase-Ab (E-301) or LOF-sialidase-Ab

References

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