Microglia-specific disruption of sialic acid-Siglec-9/E interactions: A novel immunotherapy against glioblastoma?

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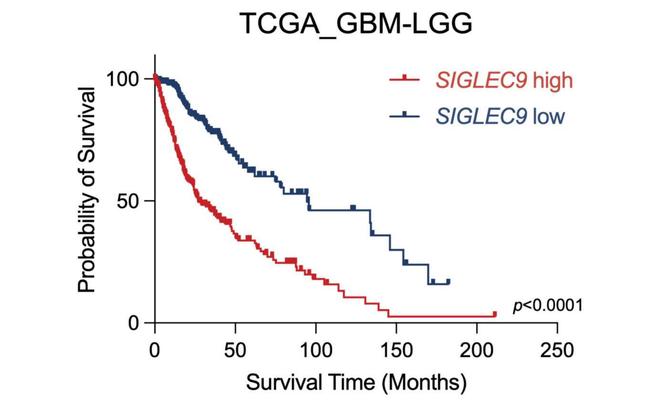
INTRODUCTION

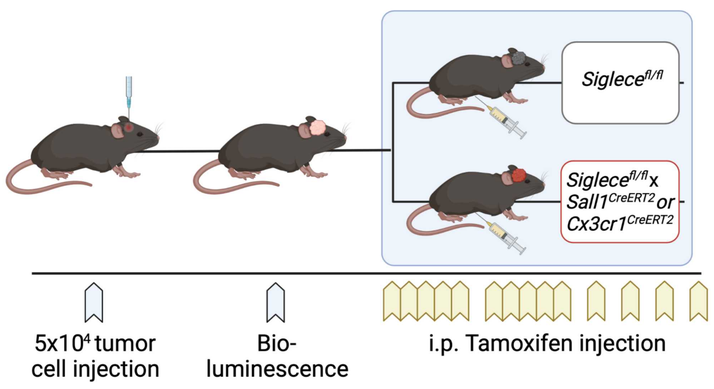
Recently, **'don't eat me'-signals** like CD47 have emerged as novel innate immune checkpoints, enabling cancer cells to evade clearance by phagocytes such as **monocyte-derived cells (MdCs)** or **microglia (MG)**. Here, we aim at defining the role of **inhibitory Siglec-9** in human and its **mouse homologue Siglec-E** in MG-centered immunotherapy against GBM.



scRNAseq data of human GBM samples. See Poster #124

METHODS

We employed a **CT-2A orthotopic GBM mouse model** with MG specific (***Sall1***^{CreERT2} x ***Siglece***$^{fl/fl}$) and whole innate-compartment (***Cx3cr1***^{CreERT2} x ***Siglece***$^{fl/fl}$) spatio-temporal deletion of Siglece. We applied multi-color flow cytometry, transcriptomics and proteomics analysis to decipher the immune response upon *Siglece* knockout.

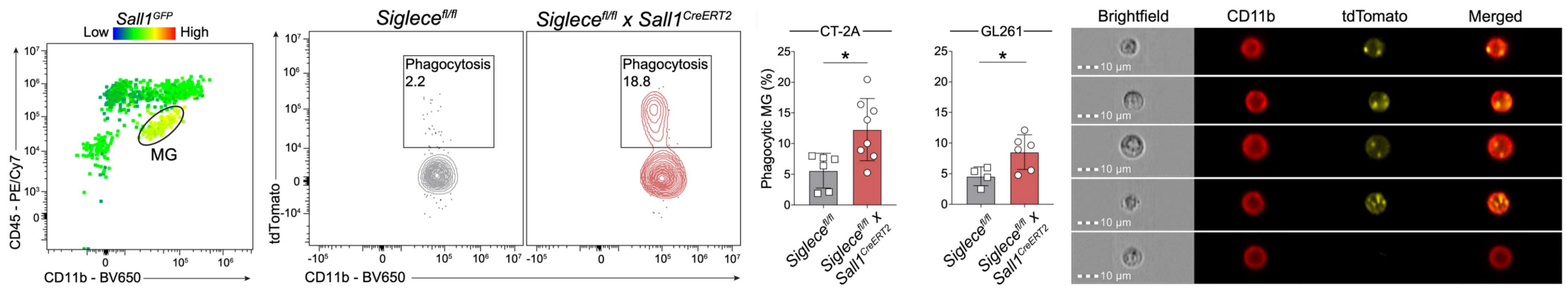


CONCLUSION

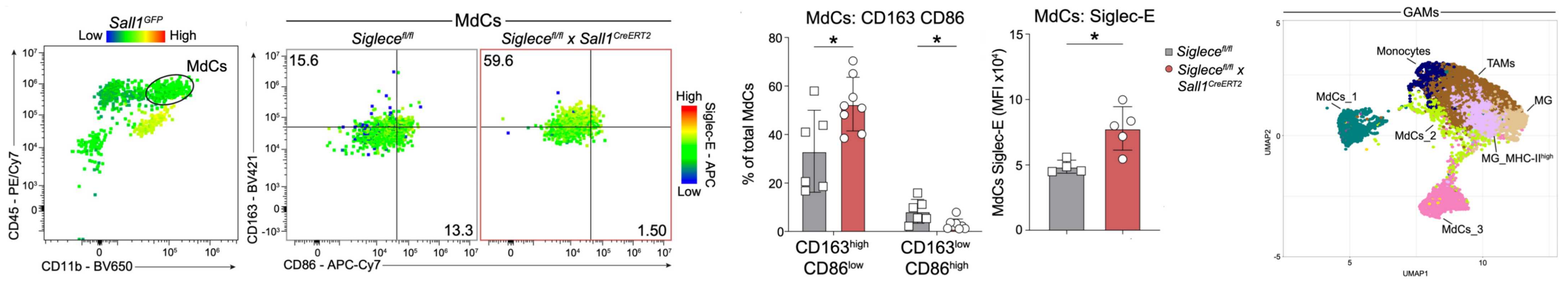
These data identify the sialic-acid-Siglec-E pathway as an anti-phagocytic signal in a pre-clinical GBM model, and demonstrate its therapeutic potential in GBM immunotherapy.

RESULTS

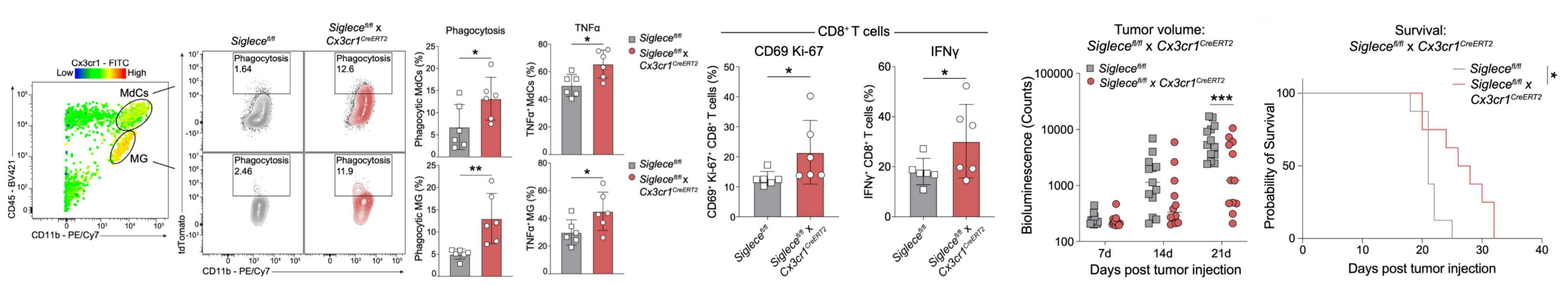
1. Conditional knockout of *Siglece* increases MG tumor-cell phagocytosis



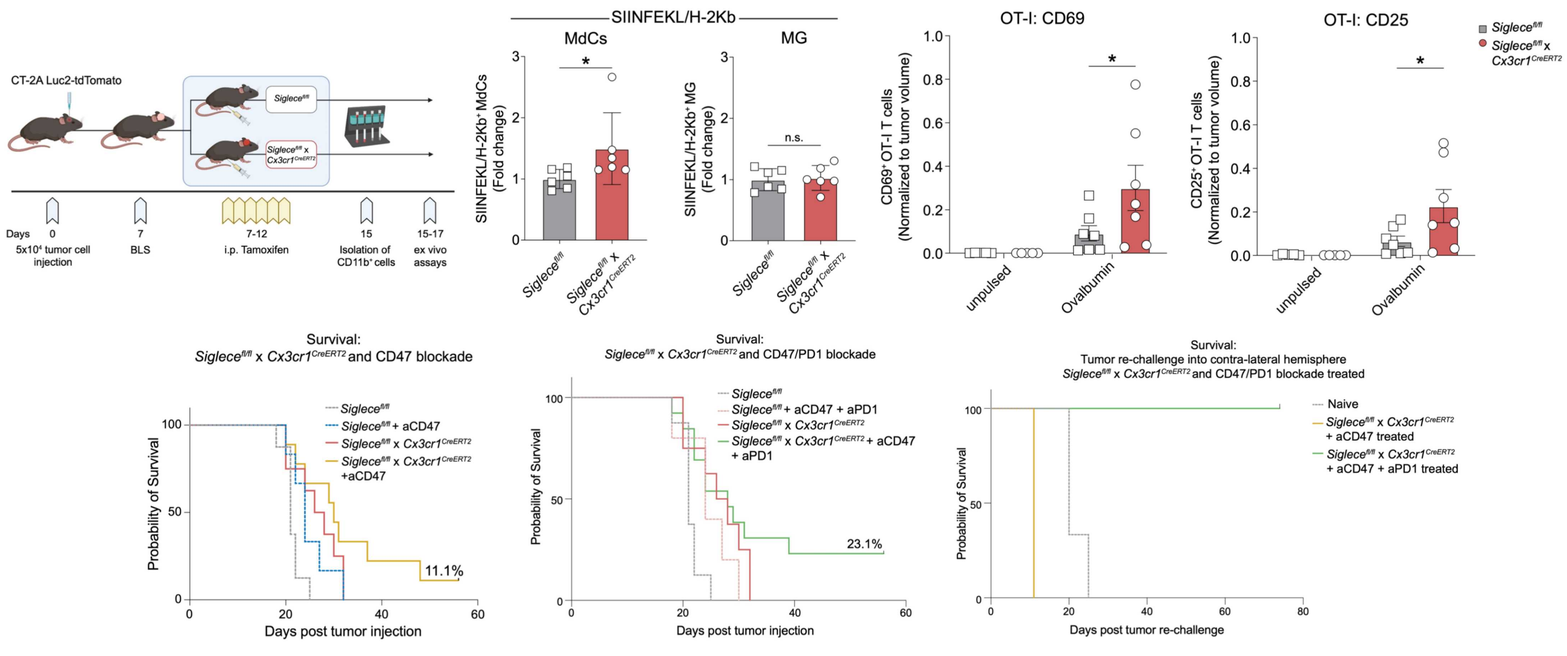
2. Increased tumor-infiltration of immunosuppressive MdCs upon MG activation



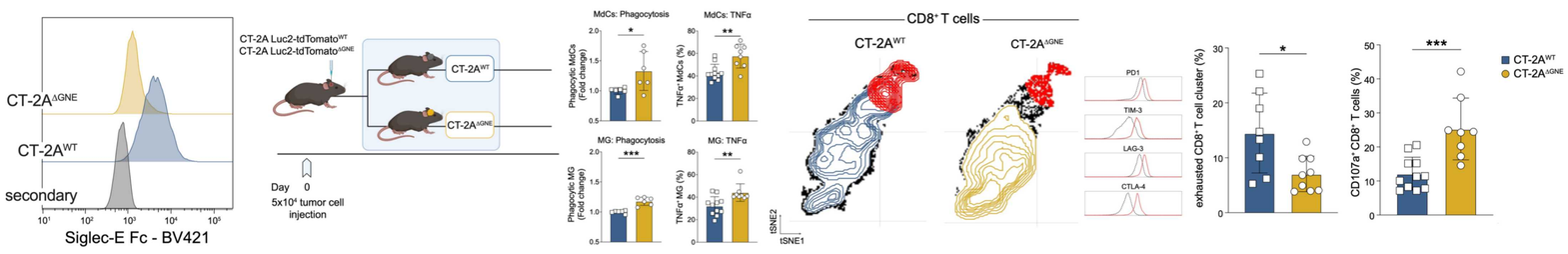
3. Extending *Siglece* knockout to MdCs (*Cx3cr1*^{CreERT2} *x Siglece*$^{fl/fl}$) renders the microenvironment anti-tumorigenic



4. MdC *Siglece* knockout induces antigen cross-presentation and cross-priming of CD8+ T cells and synergizes with innate and adaptive immunotherapies



5. Genetic targeting of sialic acids, the ligand for Siglec receptors, induces strong innate and adaptive immune response



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