Glycans' Immunomodulatory Role in Altered Glycosylation: Potential Therapeutic Target and Biomarkers

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Our group investigates the role of glycans in immunopathology, focused on diseases such as cancer and congenital disorders of glycosylation (CDG). We identified subgroups of cancer patients with aberrant sialylated glycan profiles associated with poor prognosis and immunosuppression. In triple-negative breast cancer (TNBC), patients expressing sialyl-Tn (STn) have lower overall survival. Moreover, STn+ TNBC cell lines have higher proliferation rates and decreased expression of c-myc, a regulator of proliferation and immune response. Additionally, higher expression of the *ST6GALNAC1* gene in patients positively correlates with infiltration of regulatory T cells and M2 macrophages, which are pro-tumoral and immunosuppressive. Another subgroup of high sialyl Lewis X-expressing TNBC patients also exhibited poor prognosis and higher proliferation rates. Interestingly, an anti-STn mAb that we developed overcomes immunosuppression and leverages the immune response in a preclinical breast cancer model, suggesting glycan blockade's effectiveness as a therapeutic approach in cancer.

Although sialylated glycans associate with poor cancer prognosis and immunosuppression, mechanisms underlying sialic acid deficiency remain unclear. Interestingly, we found increased Th1 profiles in models of sialic acid shortage and in GNE -CDG reinforcing the immunomodulatory role of sialic acid. In PMM2-CDG, where N-glycan defects occur, patients often experience immune-related clinical issues that worsen other symptoms. We identified altered immune-related genes and the MAPK signalling downstream to the TNF-α receptor, which may account for inefficient infections/inflammation control.

Overall, our findings highlight the importance of glycans in immunopathology and identify potential therapeutic targets and biomarkers for developing glycan-targeted therapies.

Bibliographic references:

1. Carrascal MA, ….. Santos LL, Dall'Olio F, Videira PA. Mol Oncol. 2014;8(3):753-65. doi: 10.1016/j.molonc.2014.02.008.

2. Pascoal C, Carrascal MA, … Grosso AR, Videira PA. Cancers (Basel). 2023 Jan 25;15(3):731. doi: 10.3390/cancers15030731.

3. Loureiro LR, …Palma AS, Novo C, Videira PA. Sci Rep. 2018;8(1):12196. doi: 10.1038/s41598-018-30421-w.

4. Francisco R, Pascoal C, ….Jaeken J, Grosso AR, Dos Reis Ferreira V, Videira PA. J Clin Med. 2020; 9:2092. doi: 10.3390/jcm9072092.