Globo H Expression in Metastatic Colorectal Cancer (CRC)

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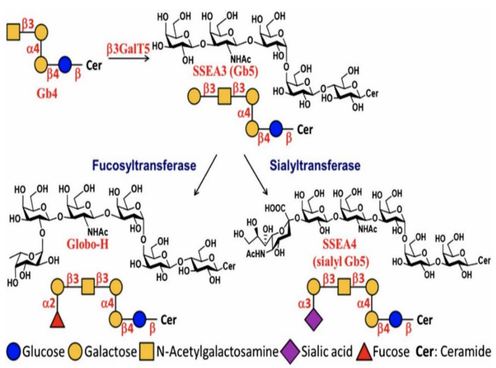
Background

- Globo H is a carbohydrate antigen that is highly expressed on the cell surface of epithelial cancers but not in normal tissue, and has been reported to correlate with poor prognosis.
- Globo H-targeted agents are being tested in early clinical trials (e.g., OBI-833, a Globo H antigen conjugated to a mutated diphtheria toxin with potential antineoplastic activities, and OBI-999, an antibody-drug conjugate (ADC) consisting of a Globo H monoclonal antibody with a synthetic antineoplastic agent).
- We aim to describe the molecular features associated with Globo H expression in CRC.



Globo H biosynthesis involves beta3GalT5, FUT1 and FUT2. Globo H enables cancer cells to escape from immune surveillance and promotes angiogenesis.

Methods

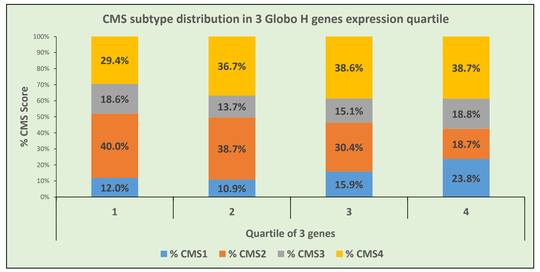
- A total of 7604 CRC tumors were tested by Caris Life Sciences (Phoenix, AZ) by NextGen DNA and RNA sequencing.
- The expression of β3GalT5, FUT-1 and FUT-2 were evaluated as surrogates for Globo H expression as they are the key enzymes in its biosynthesis.
- An average z-score of the 3 genes (GloboH) and of β3GalT5 (B3) alone were calculated; tumors with top quartile z-scores were considered expression-high (Q4) and bottom quartile, expression-low (Q1).
- QuantiSEQ was used to assess immune cell infiltration in the tumor microenvironment (TME). Statistical significance was determined using chi-square/Fisher-Exact and adjusted for multiple comparisons (q<0.05). Consensus molecular subtype (CMS) was developed using RNA seq data.

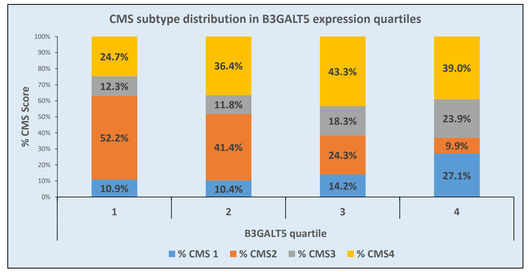
Results (continued)

1. CMS Subtype Distribution

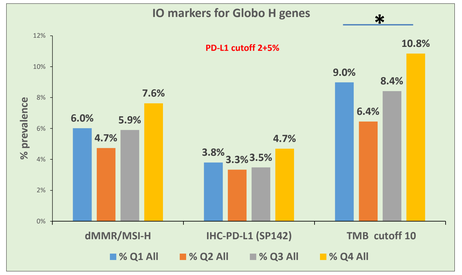
For Q1 vs Q4 all			
CMS1	CMS2	CMS3	CMS4
p<0.0001	p<0.0001	N.S.	p<0.0001

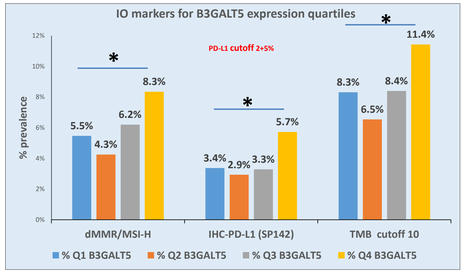
For Q1 vs Q4 B3GALT5			
CMS1	CMS2	CMS3	CMS4
p<0.0001	p<0.0001	p<0.0001	p<0.0001



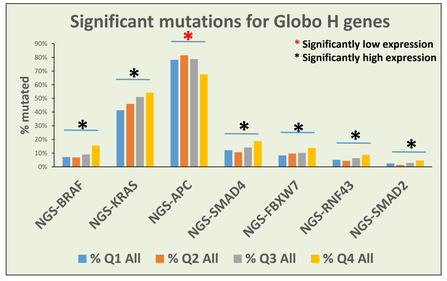


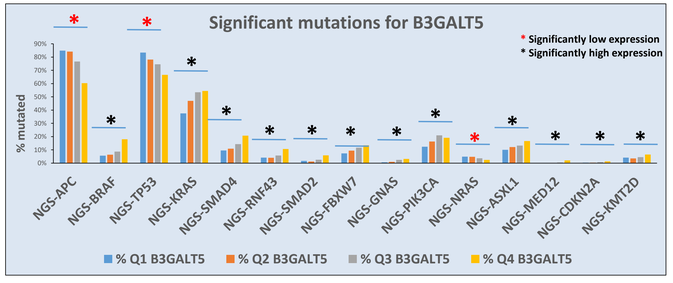
2. Markers of response to IO therapy

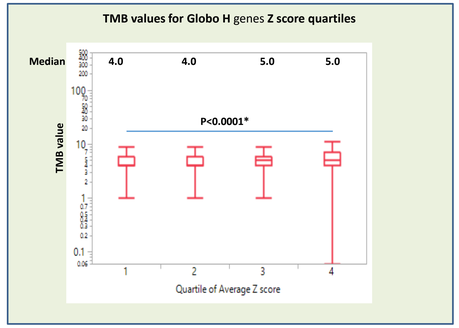


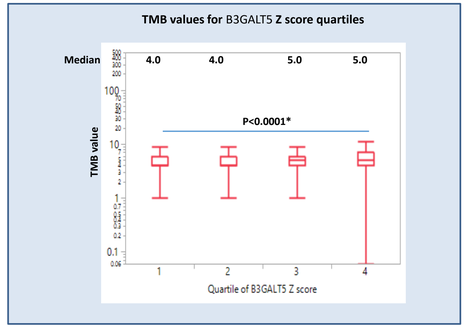


3. Significant mutations



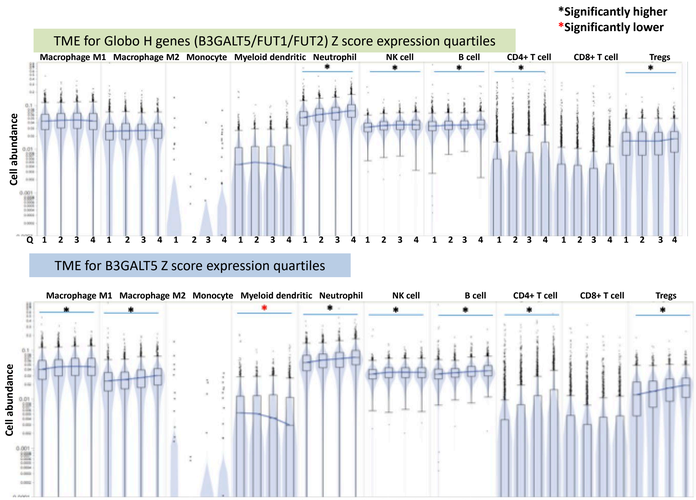






- When the 3 genes were considered, GloboH-H tumors showed higher prevalence of CMS1 and CMS4 (23.8% vs. 12%; 38.7% vs. 29.4%) and lower prevalence of CMS2 (40% vs. 18.7%) compared to GloboH-L. Similar patterns of CMS distribution were seen for B3 alone.
- B3-H tumors were significantly more frequently TMB-H (>=10) (11.4% vs. 8.3%), PD-L1 positive (5.7% vs. 3.4%) and MSI-H/dMMR (8.3% vs. 5.5%). Strong positive associations were seen with mutations in *BRAF*, *KRAS*, *RSPO3* fusion, and amplification of *cMYC* with B3 alone and GloboH (all q<0.05).
- Anti-tumor CD4+ T cells and NK cells were increased in the TME with increased expression of GloboH and B3 (q<0.05). However, immune suppressive neutrophils and Tregs were also increased. Dendritic cells were negatively associated with B3 expression while endothelial cells and fibroblasts showed a positive association with GloboH and B3.

4. Tumor Microenvironment



Globo H genes	
TME cell population	KW p value Q1 vs Q4
B cell	p<0.0001*
Macrophage 1 (M1)	0.3665
Macrophage 2 (M2)	0.0438
Monocyte	0.0428
Neutrophil	p<0.0001*
NK cell	p<0.0001*
CD4+ T cell (non-reg)	p<0.0001*
CD8+ T cell	0.5178
T regulatory (Tregs)	0.0037*
Myeloid Dendritic	0.7963
Endothelial cells	p<0.0001*
Fibroblasts	p<0.0001*

B3GALT5	
TME cell population	KW p value Q1 vs Q4
B cell	p<0.0001*
Macrophage 1 (M1)	p<0.0001*
Macrophage 2 (M2)	p<0.0001*
Monocyte	0.9851
Neutrophil	p<0.0001*
NK cell	p<0.0001*
CD4+ T cell (non-reg)	p<0.0001*
CD8+ T cell	0.8821
T regulatory (Tregs)	p<0.0001*
Myeloid Dendritic	p<0.0001*
Endothelial cells	p<0.0001*
Fibroblasts	p<0.0001*

Conclusions

- The association with TMB-H, MSI-H, and PD-L1 suggests that Globo H may be a promising target for combination therapy with immune checkpoint inhibition.
- The association with immune cell trafficking suggests manipulating the cellular balance in the TME as an approach to improve the efficacy of treatment.
- NK cell checkpoint inhibitors are in clinical trials and might be utilized in high Globo H cancers; treatments inducing DCs in tumors have been shown to enhance responses to *BRAF* and PD-L1 blockade and might be applicable in the context of Globo H immunotherapy to overcome Treg immune suppression.
- Anti-Globo H vaccines and ADCs might be particularly effective in *BRAF* and *KRAS*-mutant CRC patients.

References

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