Abstract 422682: Vulnerability to immune therapy in BRAF- and MYB-altered pediatric gliomas

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Background

- Immunological studies of pediatric gliomas are relatively rare despite being a leading cause of childhood morbidity and mortality.
- Differences that have been highlighted in studies of pediatric vs. adult brain tumor immunology include (i) low-level expression of programmed cell death protein ligand 1 (PD-L1) and (ii) the lack of prognostic significance associated with CD163+ macrophage infiltration.
- As such, it has been postulated that the pediatric brain tumor microenvironment may reflect a failure of immune surveillance rather than the establishment of an immunosuppressive one.
- We sought to define predictive signatures of immunotherapy responders by examining immune checkpoint expression, immune cell population signatures, and gene amplifications in a variety of pediatric gliomas.

Methods

- We profiled a cohort of pediatric glioma samples submitted to Caris Life Sciences (Phoenix, AZ) for analysis (N = 207). The cohort was further stratified by driver mutations: IDH mutant (N = 103), H3-3A mutant (N = 36), MYB-altered (N = 4), BRAF-altered (N = 39), and IDH wild type [IDH WT] (N = 25). De-identified next generation DNA sequencing (592-gene or whole exome) and RNA (whole transcriptome) sequencing were used to determine tumor-infiltrating immune cell signatures and immune checkpoint protein expression. Transcriptomic signatures predictive of response to immunotherapy (IFN signature score) and replication stress response defect (RSRD) score were calculated on transcripts per million (TPM) values. Immune cell fractions were estimated using RNA deconvolution (quanTIseq).

Conclusions

- BRAF- and MYB-altered gliomas displayed high immune activation relative to other tumors.
- IDH WT tumors have an immune suppressive microenvironment with relatively high immune checkpoint expression.
- Based on predictive markers, BRAF- and MYB-driven gliomas show signatures suggesting the possibility of a greater response to immunotherapies than IDH WT/mutant gliomas or H3-3A mutant gliomas.

	IDH_mut	MYB_altered	BRAF_altered	IDH_WT	H3F3a_mut
Count (N)	103	4	39	25	36
Median Age [range]	23 [12 - 25] (103)	18 [9 - 25] (4)	18 [0 - 25] (39)	21 [3 - 25] (25)	19.5 [3 - 25] (36)
Female	37.9% (39/103)	75.0% (3/4)	53.8% (21/39)	60.0% (15/25)	38.9% (14/36)
Male	62.1% (64/103)	25.0% (1/4)	46.2% (18/39)	40.0% (10/25)	61.1% (22/36)
Mutations	IDH 1: 97 IDH2: 6	MYB: 3	V600E: 23	IDH1: 0 IDH2: 0	H3F3A: 36
Fusions	IDH1: 0 IDH2: 0	MYB: 1	BRAF: 16	IDH1: 0 IDH2: 0	H3F3A: 0

	MYB-altered	BRAF-altered	IDH-Mut	IDH-WT	H3F3a-Mut
T cells CD8	0.02182	0.04349	0.00992	0.04539	0.01883
Monocytes	0.04528	0.01882	0.01036	0.00000	0.02034
Dendritic cells	0.11404	0.11194	0.12318	0.10535	0.11601
Tregs	0.10494	0.09735	0.08222	0.10467	0.09422
Neutrophils	0.10281	0.15151	0.13694	0.19948	0.14898
T cells CD4	0.04362	0.06151	0.04551	0.06494	0.03643
Macrophages M1	0.04100	0.04357	0.03712	0.03914	0.03905
B cells	0.08788	0.08814	0.08192	0.07689	0.08430
Macrophages M2	0.08627	0.08326	0.08049	0.08628	0.07964
NK cells	0.07944	0.07592	0.08031	0.07920	0.07446

High — Low

Results

	MYB-altered	BRAF-altered	IDH-Mut	IDH-WT	H3F3A-Mut
CD274	2.77	3.79	2.10	2.19	2.36
CTLA4	0.23	0.32	0.15	0.34	0.29
LAG3	0.36	0.24	0.35	0.77	0.53
IDO1	0.07	0.22	0.11	0.37	0.09
HAVCR2	28.33	28.29	19.55	25.68	20.28
CD80	0.64	0.55	0.53	1.83	0.85
CD86	6.42	11.23	6.49	7.44	5.55