The genomic, transcriptomic, and epigenomic landscape of isocitrate dehydrogenase wild-type glioblastoma across the age continuum

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BACKGROUND

- Older age is a poor prognostic factor for patients with glioblastoma (GBM).
- The incidence rate of GBM increases with age and is highest among patients 75 to 84 years old.
- The underlying biological mechanisms that contribute to poorer outcomes in older patients with GBM have not been comprehensively explored to-date.
- In the literature, established biomarkers such as MGMT promoter methylation status, PTEN-, EGFR-, and TP53-mutations do not reliably vary between older versus younger patients with GBM.

OBJECTIVE

- Identify differences in the intratumoral molecular landscape at the genomic, transcriptomic and epigenomic levels, between younger and older patients with GBM.

METHODS

- In accordance with the 2021 WHO classification scheme, we included only isocitrate dehydrogenase (IDH) wild type GBM.
- Based on published literature, we defined older as age ≥ 65.
- RNA expression, gene amplification, tumor mutational burden (TMB) and mutational profiles in patients <65 versus ≥ 65 were analyzed in three unique datasets: Tempus (n = 1,410), Caris (n = 1,432), and the Cancer Genome Atlas (TCGA) (n = 557).
- For Caris and Tempus data analyses, patient characteristics, along with molecular and sequencing data were compared at the time of tissue collection by Pearson's Chi-squared tests/Fisher's exact tests or Wilcoxon rank-sum tests, as appropriate.
- Using TCGA data, intratumoral DNA methylation, gene expression, TMB, and DNAm age acceleration were compared in older versus younger patients with GBM.

RESULTS

- There was no universal agreement between clinical databases for differences in gene expression or DNA amplification.
- TERT promoter mutations were more prevalent in patients ≥ 65 years old (Caris 82.64 vs 77.27%, p = 0.016; Tempus 58.0 vs 49.0%, p = 0.002).
- MGMT promoter methylation by PyroSeq (Caris data only) was more common in the older group (49.73 v 34.14%, p < 0.001).

Table 1. DNA amplification and mutations in older vs younger GBM

	Caris Positive (Age <65)	Caris Negative (Age <65)	Caris Positive (Age >=65)	Caris Negative (Age >=65)	Caris p-value	Tempus Positive (Age <65)	Tempus Negative (Age <65)	Tempus Positive (Age >=65)	Tempus Negative (Age >=65)	Tempus p-value	Significant Datasets
MGMT-Me	**299 (34.33%)**	**572 (65.67%)**	**261 (50.68%)**	**254 (49.32%)**	**2.04E-09**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**1**
IHC PD-L1	184 (21.45%)	674 (78.55%)	90 (17.68%)	419 (82.32%)	0.093	57 (20.0%)	230 (80.0%)	41 (21.0%)	152 (79.0%)	0.712	**0**
dMMR/MSI-H	7 (0.78%)	895 (99.22%)	8 (1.51%)	522 (98.49%)	0.188	11 (0.9%)	882 (99.1%)	1 (0.2%)	483 (99.8%)	0.067	**0**
CDK6 amplification	8 (0.89%)	890 (99.11%)	9 (1.70%)	519 (98.30%)	0.172	11 (1.2%)	904 (98.8%)	1 (0.2%)	494 (99.8%)	0.067	**0**
EGFR amplification	324 (36.04%)	575 (63.96%)	182 (34.47%)	346 (65.53%)	0.549	267 (29.0%%)	648 (71.0%)	151 (31.0%)	344 (69.0%)	0.603	**0**
NGS-EGFR	167 (18.56%)	733 (81.44%)	81 (15.31%)	448 (84.69%)	0.118	110 (12.0%)	805 (88.0%)	65 (13.0%)	430 (87.0%)	0.546	**0**
EGFRvIII mutations	197 (21.86%)	704 (78.14%)	104 (19.62%)	426 (80.38%)	0.315 (RNAseq)	87 (9.5%)	828 (90.0%)	44 (8.9%)	451 (91.0%)	0.702 (DNAseq)	**0**
EGFR Fusion	11 (1.24%)	874 (98.76%)	4 (0.76%)	520 (99.23%	0.397	45 (4.9%)	870 (95.0%)	23 (4.6%)	472 (95.0%)	0.820	**0**
MET Fusion	11 (1.22%)	890 (98.78%)	8 (1.51%)	520 (98.48%)	0.639	0 (0.0%)	915 (100%)	0 (0.0%	495 (100%)	N/A	**0**
TERT*	**697 (77.27%)**	**205 (22.73%)**	**438 (82.64%)**	**92 (17.36%)**	**0.016**	**452 (49.0%)**	**463 (51.0%)**	**288 (58.0%)**	**207 (42.0%)**	**0.002**	**2**
NGS-PTEN	268 (30.77%)	603 (69.23%)	182 (35.0%)	338 (65.0%)	0.103	261 (29.0%	654 (71.0%)	144 (29.0%)	351 (71.0%)	0.823	**0**
NGS-TP53	258 (28.67%)	642 (71.33%)	170 (32.14%)	359 (67.86%)	0.167	170 (19.0%)	745 (81.0%)	77 (16.0%)	418 (84.0%)	0.154	**0**
NGS-NF1	131 (14.57%)	768 (85.43%)	79 (14.96%)	449 (85.04%	0.841	99 (11.0%)	816 (89.0%)	59 (12.0%)	436 (88.0%)	0.532	**0**

RESULTS

Table 2. Gene expression in older vs younger GBM

Gene	Caris <65, N=902	Caris >=65, N=530	Caris p-value	Tempus <65, N=616 (log10)	Tempus >=65, N=347 (log10)	Tempus p-value	Significant Datasets
LAG3	0.38	0.41	0.544	1.50	1.44	<0.0001	**1**
PDCD1	0.30	0.33	0.144	1.62	1.62	0.935	**0**
CD274	3.74	3.61	0.369	1.87	1.9	0.444	**0**
CD3E	0.65	0.59	0.098	1.27	1.24	0.922	**0**
TNFRSF18	0.26	0.25	0.724	1.41	1.40	0.251	**0**
CD40	2.14	2.10	0.291	1.95	1.93	0.099	**0**
CD8A	0.69	0.61	0.226	1.15	1.11	0.690	**0**
TNFRSF4	0.46	0.43	0.278	1.84	1.80	0.120	**0**
IDO1	0.31	0.23	0.002	0.90	0.89	0.939	**1**
CTLA4	0.30	0.29	0.076	1.17	1.18	0.840	**0**
HAVCR2	32.44	31.37	0.637	2.83	2.85	0.061	**0**
TNFSF9	0.22	0.20	0.116	0.98	0.96	0.817	**0**
CDKN2A	1.97	2.03	0.945	1.84	1.75	0.044	**0**

TCGA

- TGCA data demonstrated that gene expression, TMB, and methylation did not change significantly with age.
- Additionally, PCOLCE2 and SLC10A4 **(Fig.1)** were differentially methylated, and missense mutations, of any type, were more common in the older group (p=0.006).
- Compared to patients ≥65 years old, DNAm age acceleration is increased in patients <65 years old (p=0.0022) **(Fig.2).**

Figure 1.

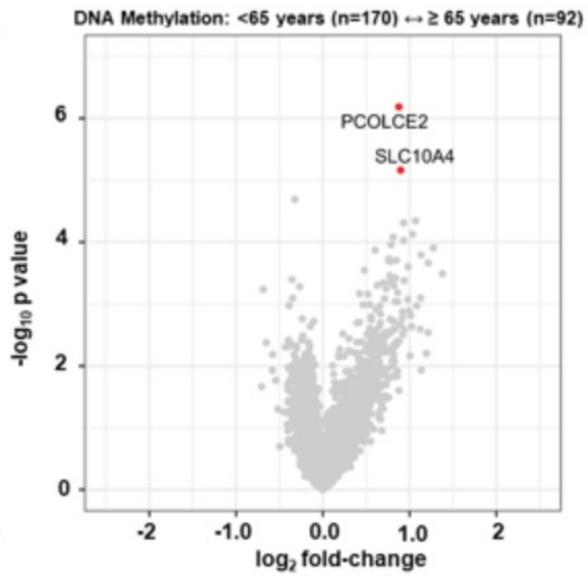
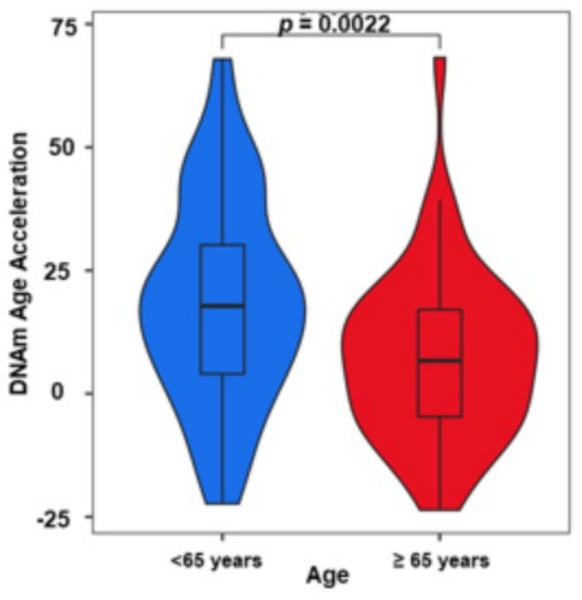


Figure 2.



CONCLUSIONS

- Despite worse survival outcomes for older patients with GBM compared to younger counterparts, the molecular landscape is similar at the genomic, transcriptomic and epigenomic levels.
- TERT promoter mutations are more common in older patients, while MGMT promoter methylation *may* be more common, it will require further validation.
- Further investigation into PCOLCE2 and SLC10A4 is warranted. However, it's unlikely that this isolated difference can fully account for poorer outcomes in older GBM.
- We hypothesize that poorer survival in older patient with GBM is not likely to be attributable solely to intratumoral factors.