



Research article

Aggrephagy-related gene signature correlates with survival and tumor-associated macrophages in glioma: Insights from single-cell and bulk RNA sequencing

Xiaowei Zhang^{1,†}, Jiayu Tan^{1,†}, Xinyu Zhang¹, Kritika Pandey², Yuqing Zhong¹, Guitao Wu³ and Kejun He^{1,*}

¹ The First Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China

² Virginia Commonwealth University, USA

³ Guangzhou Women and Children's Hospital, Guangzhou, China

***Correspondence:** Email: Hekej3@mail.sysu.edu.cn; Tel: +86-20-87338218.

† These two authors contributed equally.

Supplementary

Table S1. Baseline characteristics of glioma patients in training and validation cohorts.

Characteristic	Training Cohort	Validation Cohorts	
	TCGA	CGGA-325	CGGA-693
n	669	313	657
Age, median (IQR)	46 (34, 59)	42 (36, 51)	43 (35, 52)
Gender, n (%)			
Female	283 (42.3%)	116 (37.1%)	283 (43.1%)
Male	386 (57.7%)	197 (62.9%)	374 (56.9%)

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Characteristic	Training Cohort	Validation Cohorts	
	TCGA	CGGA-325	CGGA-693
WHO grade, n (%)			
2	215 (32.1%)	98 (31.3%)	172 (26.2%)
3	237 (35.4%)	74 (23.6%)	248 (37.7%)
4	160 (23.9%)	137 (43.8%)	237 (36.1%)
NA	57 (8.5%)	4 (1.2%)	0
IDH status, n (%)			
Mutant	423 (63.2%)	167 (53.4%)	333 (50.7%)
Wild type	237 (35.4%)	145 (46.3%)	276 (42.0%)
NA	9 (1.3%)	1 (0.3%)	48 (7.2%)
1p/19q status			
Codeletion	167 (25.0%)	62 (19.8%)	137 (20.9%)
Non-codeletion	496 (74.1%)	243 (77.6%)	454 (69.1%)
NA	6 (0.9%)	8(2.6%)	66 (10.0%)
Pathology, n (%)			
Astrocytoma	167 (25.0%)	112 (35.8%)	254 (38.7%)
Glioblastoma	160 (23.9%)	137 (43.8%)	237 (36.1%)
Oligodendroglioma	112 (16.7%)	12 (3.8%)	29 (4.4%)
Olidendroastrocytoma	173 (25.9%)	48 (15.3%)	137 (20.9%)
NA	57 (8.5%)	4 (1.3%)	0
MGMT _p status			
Methylation	473 (70.7%)	152 (48.6%)	304 (46.3%)
Unmethylation	162 (24.2%)	143 (45.7%)	218 (33.2%)
NA	34 (5.1%)	18 (5.8%)	135 (20.5%)
KPS score, n (%)			
>80	199 (29.7%)	NA	NA
≤80	179 (26.8%)	NA	NA
NA	291 (43.5%)	NA	NA

Table S2. The 44 ARGS in the study.

ENTREZ ID	SYMBOL	ENTREZ ID	SYMBOL
200,894	ARL13B	113,457	TUBA3D
1068	CETN1	112,714	TUBA3E
1080	CFTR	7277	TUBA4A
1778	DYNC1H1	80,086	TUBA4B
1780	DYNC1H1	51,807	TUBA8
1781	DYNC1I2	79,861	TUBAL3
51,143	DYNC1LI1	81,027	TUBB1
1783	DYNC1LI2	7280	TUBB2A

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ENTREZ ID	SYMBOL	ENTREZ ID	SYMBOL
8655	DYNLL1	347,733	TUBB2B
140,735	DYNLL2	10,381	TUBB3
10,013	HDAC6	10,382	TUBB4A
3297	HSF1	10,383	TUBB4B
3320	HSP90AA1	84,617	TUBB6
8100	IFT88	347,688	TUBB8
11,315	PARK7	260,334	TUBB8B
5116	PCNT	7311	UBA52
5071	PRKN	7314	UBB
6233	RPS27A	7316	UBC
7846	TUBA1A	7334	UBE2N
10,376	TUBA1B	7335	UBE2V1
84,790	TUBA1C	7415	VCP
7278	TUBA3C	7431	VIM

Table S3. Transcriptional predictors of immunotherapy response.

Proxy of response	Original study	Description	Signature genes	Association with immune response
Cytolytic activity (CYT)	Rooney et al, Cell, 2015	Two cytolytic effector genes: granzyme A (GZMA) and perforin-1 (PRF1).	GZMA, PRF1	Positive
Roh immune score (Roh_IS)	Roh et al., Sci. Transl. Med., 2017	Genes related to cytolytic markers, HLA molecules, IFN- γ pathway, selected chemokines, and adhesion molecules.	GZMA, GZMB, PRF1, GNLY, HLA-A, HLA-B, HLA-C, HLA-E, HLA-F, HLA-G, HLA-H, HLA-DMA, HLA-DMB, HLA-DOA, HLA-DOB, HLA-DPA1, HLA-DPB1, HLA-DQA1, HLA-DQA2, HLA-DQB1, HLA-DRA, HLA-DRB1, IFNG, IFNGR1, IFNGR2, IRF1, STAT1, PSMB9, CCR5, CCL3, CCL4, CCL5, CXCL9, CXCL10, CXCL11, ICAM1, ICAM2, ICAM3, ICAM4, ICAM5, VCAM1	Positive

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Proxy of response	Original study	Description	Signature genes	Association with immune response
Chemokine signature (chemokines)	Messina et al., Nat. Sci. Rep., 2012	Immune- and inflammation related 12 chemokine genes.	CCL2, CCL3, CCL4, CCL5, CCL8, CCL18, CCL19, CCL21, CXCL9, CXCL10, CXCL11, CXCL13	Positive
Davoli immune signature (Davoli_IS)	Davoli et al., Science 2017	Gene markers of cytotoxic immune cell infiltrates (cytotoxic CD8+ T cells and NK cells).	CD247, CD2, CD3E, GZMH, NKG7, PRF1, GZMK	Positive
IFN γ signature (IFN γ)	Ayers et al., JCI, 2017	Genes related to IFN- γ signaling.	IFNG, STAT1, CXCL9, CXCL10, IDO1, HLA-DRA	Positive
Expanded immune signature (Ayers_expIS)	Ayers et al., JCI, 2017	Genes associated with cytolytic activity, pro-inflammatory cytokines/chemokines, T cell markers, NK cell activity, antigen presentation and T cell checkpoints.	GZMB, GZMK, CXCR6, CXCL10, CXCL13, CCL5, STAT1, CD3D, CD3E, CD2, IL2RG, NKG7, HLA-E, CIITA, HLA-DRA, LAG3, IDO1, TAGAP	Positive

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Proxy of response	Original study	Description	Signature genes	Association with immune response
T-cell inflamed signature (Tcell_inflamed)	Ayers et al., JCI, 2017	This signature represents the biology of a T-cell inflamed microenvironment including IFN- γ responsive genes related to antigen presentation, chemokine expression, cytotoxic activity, and adaptive immune resistance.	CCL5, CD27, CD274 (PD-L1), CD276 (B7-H3), CD8A, CMKLR1, CXCL9, CXCR6, HLA-DQA1, HLA-DRB1, HLA-E, IDO1, LAG3, NKG7, PDCD1LG2 (PDL2), PSMB10, STAT1, TIGIT	Positive
Tumor immune dysfunction and exclusion (TIDE)	Jiang et al., Nat. Med., 2018	Predictor based on two tumor immune escape mechanisms such as T cell exclusion and dysfunction.	Used published framework	Negative (Patients with higher TIDE scores had a higher chance of antitumour immune escape, thereby indicating a lower immunotherapy response rate.)
Tertiary lymphoid structures signature (TLS)	Cabrita et al., Nature, 2020	Signature based on differentially expressed genes in tumors with tertiary lymphoid structures.	CD79B, CD1D, CCR6, LAT, SKAP1, CETP, EIF1AY, RBP5, PTGDS	Positive

Table S4. Comparison of the concordance index (C-index) between ARPS and other clinical characteristic in predicting overall survival.

	TCGA	CGGA-325	CGGA-693
ARPS	0.825 ± 0.013	0.693 ± 0.016	0.642 ± 0.015
Age	0.665 ± 0.016	0.526 ± 0.009	0.541 ± 0.009
IDH	0.785 ± 0.012	0.622 ± 0.017	0.655 ± 0.012
1p/19q	0.613 ± 0.012	0.618 ± 0.014	0.613 ± 0.01
MGMTp status	0.657 ± 0.018	0.524 ± 0.019	0.52 ± 0.015
Grade	0.789 ± 0.013	0.722 ± 0.014	0.699 ± 0.012

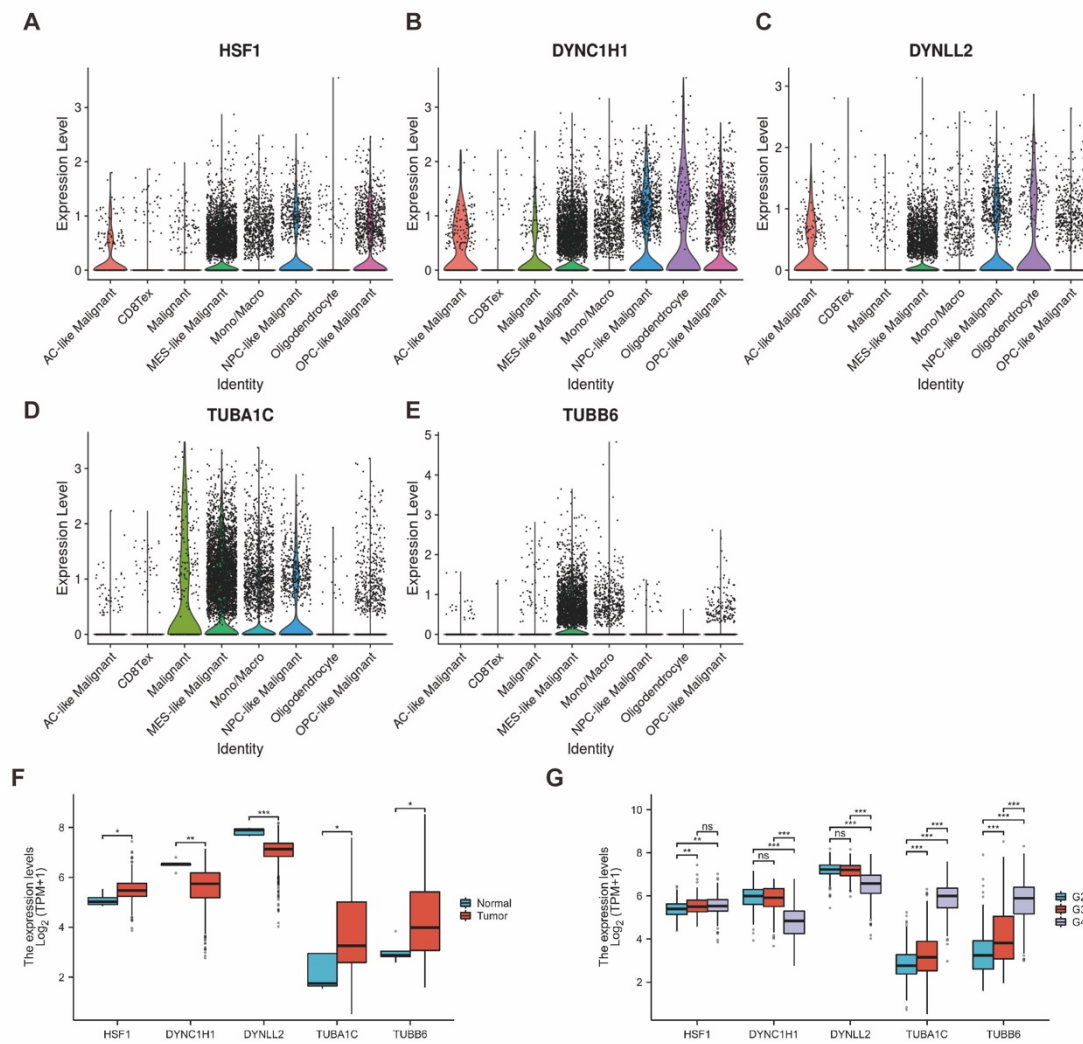


Figure S1. The expression pattern of selected ARGs. A–E. The expression of 5 ARGs in different cell types in GSE131928 10X dataset. F. The expression of 5 ARGs in glioma tissues of TCGA-GBMLGG cohort and 1152 normal brain tissues from GTEx dataset. G. The expression of 5 ARGs in different grade of gliomas in TCGA-GBMLGG cohort.

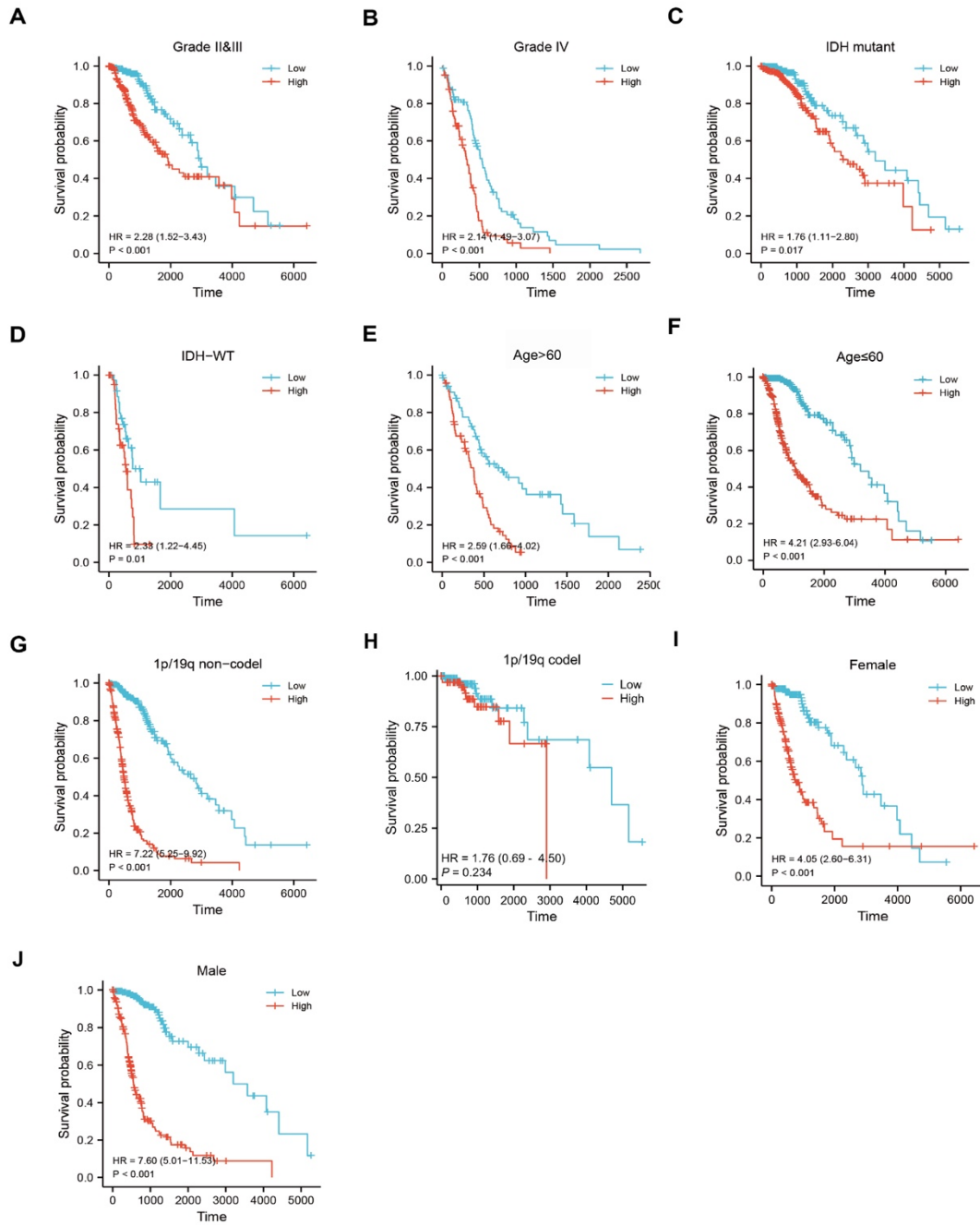


Figure S2. Subgroup Kaplan-Meier analysis of ARPS in TCGA-GBMLGG cohort. A. Grade 2&3; B. Grade 4. C. IDH mutant; D. IDH-WT; E. Age > 60; F. Age ≤ 60; G. 1p/19q non-codeletion; H. 1p/19q codeletion; I. Female; J: Male.

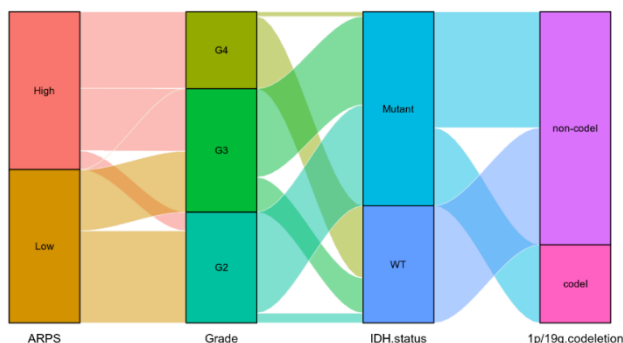


Figure S3. The Sankey diagram illustrates the relationship between ARPS and the tumor grade, molecular characteristics of the patients in TCGA-GBMLGG cohort.



Figure S4. Immune infiltration of high and low ARPS groups analyzed by multiple algorithms, including TIMER, EPIC, MCPcounter, xCell, and quantiseq.



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