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Germline polymorphisms in myeloid-associated genes are not associated with survival in glioma patients

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Abstract

Immune cells of myeloid origin, including microglia, macrophages, and myeloid-derived suppressor cells adopt immunosuppressive phenotypes that support gliomagenesis. Here, we tested an *a priori* hypothesis that single nucleotide polymorphisms (SNPs) in genes related to glioma-associated myeloid cell regulation and function are also associated with patient survival after glioma diagnosis. Subjects for this study were 992 glioma patients treated at The University of Texas MD Anderson Cancer Center in Houston, Texas between 1992 and 2008. Haplotype-tagging SNPs in 91 myeloid-associated genes were analyzed for association with survival by Cox regression. Individual SNP- and gene-based tests were performed separately in glioblastoma (WHO grade IV, n=511) and lower-grade glioma (WHO grade II-III, n=481) groups. After adjustment for multiple testing, no myeloid-associated gene variants were significantly associated with survival in glioblastoma. Two SNPs, rs147960238 in *CD163* ($p=2.2 \times 10^{-5}$) and rs17138945 in *MET* ($p=5.6 \times 10^{-5}$) were significantly associated with survival of patients with lower-grade glioma. However, these associations were not confirmed in an independent analysis of 563 lower-grade glioma cases from the University of California at San Francisco Adult Glioma Study

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COMPLIANCE WITH ETHICAL STANDARDS

Conflict of Interest: All of the authors have declared no conflicts of interest.

Ethical Approval and Informed Consent: This study was approved by the Institutional Review Boards of MD Anderson, Baylor College of Medicine, and University of California, San Francisco, and written informed consent was obtained from each participant. All procedures performed were in accordance with the ethical standards of the institutional research committees and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

(p=0.65 and p=0.41, respectively). The results of this study do not support a role for inherited polymorphisms in myeloid-associated genes in affecting survival of patients diagnosed with glioblastoma or lower-grade glioma.

Keywords

Myeloid-derived suppressor cells; macrophages; microglia; immune suppression; glioma; glioblastoma; survival; genetic polymorphism

INTRODUCTION

Gliomas, which account for approximately 75% of primary malignant brain tumors [1], exist in a dynamic microenvironment that influences tumor development and ultimately patient survival. Although gliomas are highly infiltrated by immune cells of the myeloid lineage including microglia, macrophages, and myeloid-derived suppressor cells (MDSCs; collectively, glioma-associated myeloid cells), these cells have been shown to adopt immunosuppressive and tumor-supportive phenotypes in response to tumor-secreted signals [2–5]. Furthermore, the degree of myeloid-derived cell infiltration has been shown to correlate with glioma grade in human specimens and survival in mouse models of glioma [6–8]. Given these observations, we hypothesized that germline polymorphisms in genes central to the function of glioma-associated myeloid cells may be associated with the prognosis of patients with glioblastoma or lower-grade glioma.

MATERIALS AND METHODS

Study subjects and data collection

Participants in the discovery population for this study included 992 adult glioma patients of Caucasian ethnicity (ICD-O-3 codes 9380-9340) diagnosed and treated at The University of Texas MD Anderson Cancer Center (MD Anderson) in Houston, Texas from 1992 to 2008 [9, 10]. Treatment and survival data (dates of death or last contact) were collected retrospectively from medical record review through August 2016, and dates of death were confirmed by querying the Social Security Death Index (a database created from the United States Social Security Administration’s Death Master File). Glioblastoma patients were restricted to those who received both chemotherapy and radiotherapy. The study was approved by the Institutional Review Boards of both MD Anderson and Baylor College of Medicine, and written informed consent was obtained from each participant. An independent population of 563 patients with lower-grade glioma who were included in the University of California at San Francisco Adult Glioma Study [11] served as a validation set for this analysis.

Selection of genes, SNPs, and genotyping assays

We identified genes related to the biology of glioma-associated myeloid cells for analysis in this study. In total, 91 genes were selected based on a systematic review of the literature by our research group and included those encoding transcription factors, cytokines and chemokines, receptors, enzymes, and other genes as previously described for which

genotyping data were available [12] (Table 1). Genotyping for the discovery population was conducted using the Illumina Human 610-Quad Bead Chip platform, and genotype imputation was performed to increase genomic resolution, as previously described [9, 11]. A total of 2,040 study population-specific haplotype-tagging SNPs ($r^2 \geq 0.8$) with minor allele frequency (MAF) ≥ 1% were identified using Haploview Tagger software [13] in the 91 gene regions, plus 5 kb upstream of the selected genes.

Statistical methods

Survival time was defined as the time between pathological diagnosis and date of death, if known, or date of last contact (patients in the latter group were censored as of the date of last contact). We computed hazard ratios (HR) and 95% confidence intervals (CI) using Cox proportional hazards regression for individual SNPs of interest under an additive allelic model for glioblastoma and lower-grade glioma patient groups with P-values determined by the Wald method. Proportional hazards assumptions were checked for each variable via examination of Schoenfeld residuals and log-log survival plots; assumptions were met for all variables except for surgery among glioblastoma patients, which was remedied by performing Cox regression stratified by surgery type to allow for different baseline hazards. Glioblastoma models were adjusted for age and sex, whereas lower-grade glioma models were adjusted for age, sex, extent of surgery (gross total/partial/biopsy), chemotherapy (yes/no), and radiotherapy (yes/no). Gene-based tests were performed using the CoxKM method [14], and all analyses were performed using R (https://www.r-project.org). Adjustment for multiple comparisons was performed by calculation of False Discovery Rate (FDR)-adjusted p values according to the method of Benjamini and Hochberg [15].

RESULTS

Discovery set patient characteristics

Characteristics for the glioblastoma (WHO grade IV) and lower-grade glioma (WHO grade II–III) discovery set populations are presented in Table 2A and Table 2B, respectively. As of August 2016, a date of death was known for 458 of 511 (89.6%) glioblastoma patients and 299 of 481 (62.2%) lower-grade glioma patients, and the median survival times (MSTs) were 1.6 and 6.8 years, respectively. Approximately two-thirds of patients in both groups were male, and the mean age at diagnosis was 52.6 years for glioblastoma subjects and 40.4 years for lower-grade glioma subjects. At the univariate level, sex, age at diagnosis, and extent of surgery were each statistically significantly-associated with survival of glioblastoma, whereas age at diagnosis, tumor grade, tumor histology, extent of surgery, and treatment with radiotherapy and chemotherapy were each associated with survival of lower-grade glioma.

Myeloid-associated gene variants and survival

Haplotype-tagging SNPs (n=2,040) in 91 myeloid-associated genes were evaluated for association with glioma survival. All individual SNP associations with survival in patients with glioblastoma and lower-grade glioma are illustrated in Figure 1, and the results for the top-associated SNPs in each glioma subtype are presented in Table 3. The SNP most strongly associated with survival of glioblastoma patients was rs147177288 in *NFKB1*

(HR=2.53; 95% CI: 1.47–4.37; p=8.7x10^{-4}); however, this association was not significant after adjustment for multiple testing (FDR-adjusted p=0.73). In the lower-grade glioma analysis, five SNPs were associated with survival at p<0.001, two of which remained significant after adjustment for multiple comparisons (FDR-adjusted p<0.10). The results indicated inferior survival for carriers of the C allele at rs147960238 in *CD163* (HR=5.47, 95% CI: 2.49–11.99, p=2.2x10^{-5}, FDR-adjusted p=0.046) and for carriers of the G allele at rs17138945 in *MET* (HR=2.27, 95% CI: 1.52–3.38, p=5.6x10^{-5}, FDR-adjusted p=0.057). In gene-based analyses, the strongest associations with survival in patients with glioblastoma and lower-grade glioma were observed for *IL6* (p=0.013) and *STAT3* (p=0.034), respectively; however, neither was significant after correction for the 91 genes analyzed.

Replication results

Associations between rs147960238 and rs17138945 and survival of lower-grade glioma were evaluated in an independent cohort of 563 patients with grade II and grade III glioma participating in the University of California at San Francisco Adult Glioma Study [11]. The median survival time for this population was 9.6 years, and dates of death were recorded for 274 (48.7%) of the subjects. The median age at diagnosis was 44 years, and 57% of subjects were male. The distribution of tumor histologies did not differ significantly from those in the discovery set (p=0.20). Minor allele frequencies for rs147960238 (0.014) and rs17138945 (0.042) were consistent with the discovery set population. When tested under the same model as employed in the discovery analysis, these variants were not associated with lower-grade glioma survival (rs147960238: HR=0.82, 95% CI: 0.36–1.88, p=0.65; rs17138945: HR=0.84; 95% CI: 0.56–1.27; p=0.41).

DISCUSSION

Gliomas have been shown to inhibit effective antitumor immune responses via a variety of local and systemic immunosuppressive mechanisms [16, 17]. Myeloid-derived immune cells including microglia, macrophages, and MDSCs are potent mediators of this immunosuppressive activity [18–20]. In this study, we sought to test the specific hypothesis that polymorphisms in genes involved in the immunosuppressive behavior of glioma-associated myeloid cells are associated with survival of patients with glioblastoma or lower-grade glioma.

An analysis of 511 glioblastoma patients did not provide support for our hypothesis at the individual SNP- or gene-level. In an analysis of 481 lower-grade glioma patients, rs147960238, which is located in the 10th intron of *CD163,* and rs17138945, which is located in the 2nd intron of *MET*, were significantly associated with survival. *CD163* is a hemoglobin/haptoglobin complex receptor that is expressed on macrophages and microglia and may play a role in macrophage-mediated anti-inflammatory responses [21, 22]. *MET* is a receptor tyrosine kinase and proto-oncogene that is also involved in the expansion of MDSC populations [23]. The associations observed at these genes were not reproduced in an independent analysis of 563 patients with lower-grade glioma who participated in the University of California at San Francisco Adult Glioma Study. It is plausible that detection of these effects in the replication set was hindered by differences between study populations

such as in treatment received or in the underlying molecular subtypes of glioma. We were unable to control for treatment variables with greater specificity due to limitations of the data available. However, the associations observed with the low-frequency variants at rs147960238 and rs17138945 in the discovery population may also be attributable to chance, highlighting the importance of independent validation in studies of this nature.

Taken together, although the immunosuppressive effects of glioma-associated myeloid cells are well-documented, the results of this study do not support a significant role for inherited genetic variation in genes governing this behavior in survival of glioma patients. Notably, a similar conclusion was reached in a recent analysis of variants in myeloid-derived suppressor cell pathway genes and survival of ovarian cancer patients [24]. Our study had ≥80% power at α=0.05/2,040=2.45x10^{-5} to detect hazard ratios of at least 1.42 and 1.78 in the glioblastoma analysis and 1.53 and 1.94 in the lower-grade glioma analysis in variants with minor allele frequencies of 40% and 10%, respectively. Thus, it is plausible that associations may exist with smaller effect sizes and/or with rare variants; it is also possible that associations were missed in genes involved in myeloid cell regulation that were not included for analysis in our study. However, this study did not detect reproducible associations between polymorphisms in known myeloid-associated genes and survival in glioma patients, despite sufficient statistical power to detect moderate and large effects.

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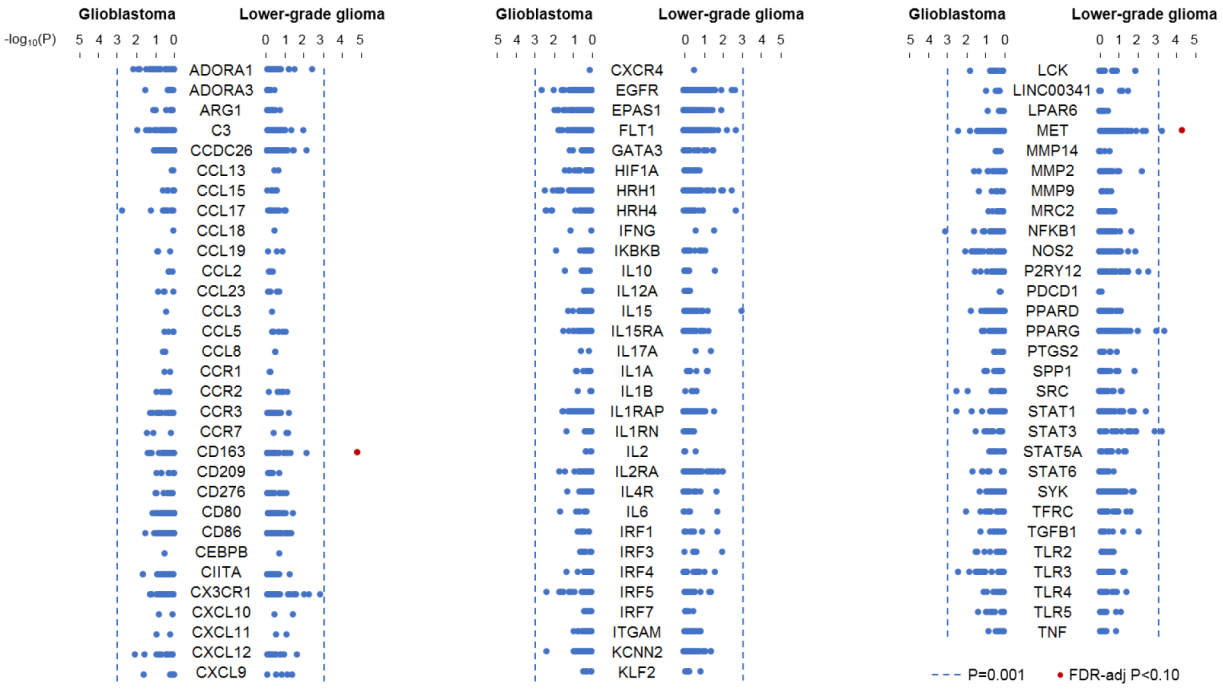

Figure 1.

Association of variants in myeloid-associated genes with survival in glioma patients. Dots represent SNPs tested for association in the corresponding myeloid-associated gene with survival of glioblastoma patients or lower-grade glioma patients, and they are plotted according to the $-\log_{10}$(p value) from single-SNP tests. A significance level of p = 0.001 is denoted by the dotted line, and SNPs with False Discovery Rate-adjusted p values < 0.10 are colored in red.

Table 1

Myeloid-associated genes selected for study

Functional group	n	Genes included
Transcription factors	17	*HIF1A, HIF2A/EPAS1, NFKB1, IRF1, IRF3, IRF4, IRF5, IRF7, STAT1, STAT3, STAT5A, STAT6, KLF2, PPARD, PPARG, CEBPB, GATA3*
Cytokines & chemokines	25	*IL1A, IL1B, IL2, IL6, IL10, IL12A, IL15, IL17A, TNF, TGFB1, IFNG, CCL2, CCL5, CCL8, CCL13, CCL15, CCL17, CCL18, CCL19, CCL23, CXCL9, CXCL10, CXCL11, CXCL12, MIP1A/CCL3*
Receptors	26	*IL1RN, IL1RAP, IL2RA, IL4R, IL15RA, HRH1, HRH4, TFRC, EGFR, VEGFR1/FLT1, MET, CCR1, CCR2, CCR3, CCR7, TLR2, TLR3, TLR4, TLR5, ADORA1, ADORA3, P2RY5/LPAR6, P2RY12, CXCR4, CX3CR1, CR3/ITGAM*
Enzymes	6	*ARG1, NOS2, PTGS2, SYK, LCK, SRC*
Others	17	*SPP1, IKBKB, MT1MMP/MMP14, MMP2, MMP9, CIITA, C3, CD209, CD280/MRC2, CD279/PDCD1, CD276, CD163, CD80, CD86, CCDC26, C14orf139/LINC00341, KCNN2*

Table 2A

Characteristics of glioblastoma study subjects

Characteristic	N (%)	MST (y)	HR (95% CI)	P
Total/events	511/458	1.6		
Sex				0.041
Female	185 (36.2)	1.8	Reference	
Male	326 (63.8)	1.5	1.22 (1.01–1.48)	
Age at diagnosis (y)				<0.001
Mean ± SD	52.6 ± 11.7			
18–39	66 (12.9)	2.7	Reference	
40–69	408 (79.8)	1.5	2.03 (1.52–2.72)	
70+	37 (7.2)	1.7	2.12 (1.38–3.26)	
Surgery				<0.001
Gross-total resection	167 (32.7)	2.0	Reference	
Partial resection	161 (31.5)	1.4	1.57 (1.24–1.97)	
Biopsy only	82 (16.0)	1.2	1.83 (1.39–2.40)	
Unknown	101 (19.8)			

SD: standard deviation; MST: median survival time; HR: hazard ratio

Table 2B

Characteristics of lower-grade glioma study subjects

Characteristic	N (%)	MST (y)	HR (95% CI)	P
Total/events	481/299	6.8		
Sex				0.20
Female	180 (37.4)	8.4	Reference	
Male	301 (62.6)	6.4	1.17 (0.92–1.48)	
Age at diagnosis (y)				<0.001
Mean ± SD	40.4 ± 12.2			
18–39	251 (52.2)	8.3	Reference	
40–69	223 (46.4)	4.8	1.60 (1.27–2.01)	
70+	7 (1.5)	1.2	4.43 (2.07–9.49)	
Grade				<0.001
II	145 (30.1)	10.3	Reference	
III	267 (55.5)	4.6	1.59 (1.22–2.07)	
Unknown	69 (14.3)			
Histology				<0.001
Oligodendroglioma	148 (30.8)	11.2	Reference	
Oligoastrocytoma	43 (8.9)	7.4	1.22 (0.78–1.91)	
Astrocytoma	234 (48.6)	4.6	1.81 (1.38–2.38)	
Unknown	56 (11.6)			
Surgery				<0.001
Gross-total resection	86 (17.9)	15.6	Reference	
Partial resection	133 (27.7)	6.7	1.59 (1.09–2.32)	
Biopsy only	203 (42.2)	4.8	2.08 (1.46–2.95)	
Unknown	59 (12.3)			
Radiotherapy				0.040
Yes	406 (84.4)	6.6	Reference	
No	21 (4.4)	14.4	0.50 (0.26–0.97)	
Unknown	54 (11.2)			
Chemotherapy				0.006
Yes	383 (79.6)	6.6	Reference	
No	25 (5.2)	NA	0.39 (0.20–0.77)	
Unknown	73 (15.2)			

SD: standard deviation; MST: median survival time; HR: hazard ratio

Table 3

Top SNP associations with glioma patient survival

						Discovery		Validation	
Glioma subtype	**Gene**	**rsID**	**MA**	**MAF**	**Info[1]**	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**
Glioblastoma	*NFKB1*	rs147177288	C	0.016	0.98	2.53 (1.47–4.37)	$8.69x10^{-4}$	-	-
	CCL17	rs62037107	T	0.020	0.97	2.04 (1.30–3.20)	$1.91x10^{-3}$	-	-
	EGFR	rs28557040	G	0.042	0.99	1.73 (1.21–2.48)	$2.48x10^{-3}$	-	-
	SRC	rs6017962	G	0.026	0.96	1.78 (1.21–2.62)	$3.33x10^{-3}$	-	-
	STAT1	rs113635552	C	0.016	0.85	1.82 (1.22–2.72)	$3.37x10^{-3}$	-	-
Lower-grade glioma	*CD163*	rs147960238	C	0.014	0.88	5.47 (2.49–11.99)	$2.23x10^{-5}$ *	0.82 (0.36–1.88)	0.65
	MET	rs17138945	G	0.038	0.99	2.27 (1.52–3.38)	$5.61x10^{-5}$ *	0.84 (0.56–1.27)	0.41
	PPARG	rs116793915	G	0.016	0.88	3.25 (1.68–6.29)	$4.49x10^{-4}$	-	-
	STAT3	rs139679582	A	0.012	0.90	3.00 (1.60–5.64)	$6.14x10^{-4}$	-	-
	MET	rs38841	G	0.361	1.00	0.72 (0.60–0.87)	$6.49x10^{-4}$	-	-

MA: minor allele; MAF: minor allele frequency; HR: hazard ratio

[1] Info denotes “information score” reflecting quality of genotype imputation in discovery population

* False discovery rate-adjusted p value < 0.10