Tumor-Infiltrating Lymphocytes in Glioblastoma are associated with NF1, TP53, and RB1 mutations and the Mesenchymal Subtype

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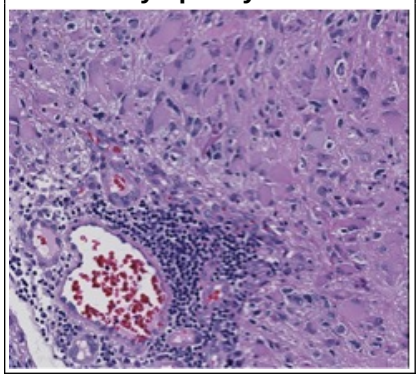
Tumor-infiltrating Lymphocytes



Introduction

Although tumor-infiltrating lymphocytes have prognostic significance in many human neoplasms, their biologic and clinical significance in glioblastoma (GBM) has not been fully defined. We hypothesized that lymphocytes in GBM are correlated with specific molecular alterations and histologies, contribute to the host immune response, and may be related to patient outcome.

Methods

Using publicly available molecular, histologic, and clinical data from The Cancer Genome Atlas (TCGA), we quantified the density of tumor-infiltrating lymphocytes in 171 cases. Histologic features were annotated as absent (0), present (1+) or abundant (2+). Associations between lymphocytes and histologic features, copy number, gene expression, and nucleotide sequence aberrations were examined by Chi-square tests. The effect of lymphocytes on survival was assessed by log-rank tests.

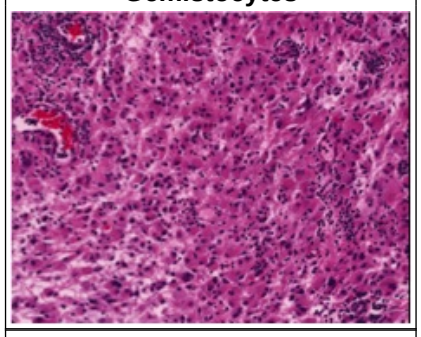
Results

We detected a positive correlation between lymphocytes and those GBMs with gemistocytes, sarcomatous cells, epithelioid cells, and giant cells. Conversely, lymphocytes were depleted in tumors characterized by small cells and oligodendroglial cells.

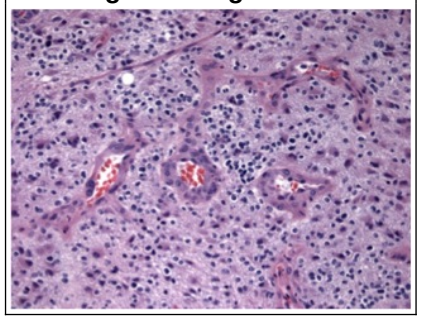
Other Histologic Features

	Prob	Correlation
Inflammation	<0.0001	0.9258
Endothelial hyperplasia	0.0536	-0.1480
Epithelial metaplasia	0.0361	0.1608
Gemistocytes	0.0047	0.2169
Giant cells	0.0188	0.1808
Sarcomatous metaplasia	0.0042	0.2194
Microvascular hyperplasia	0.5949	-0.0408
Oligodendroglial cells	0.0141	-0.1883
Small cells	0.0018	-0.2406
Satellitosis	0.2023	-0.0981

Gemistocytes



Oligodendroglial Cells



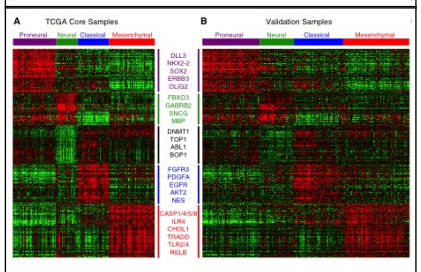
Lymphocytes were associated with NF1 deletions and mutations in NF1, TP53, and RB1 (all $p<0.05$). These molecular alterations are enriched in the gemistocytic, sarcomatous, epithelioid, and giant cell histologic subtypes.

Lymphocytes are Associated with Mutations in NF1, TP53, and RB1

	Lymphocytes		
	0, 1+, 2+	0 versus 1+, 2+	0, 1+ versus 2+
TP53	**0.0023**	**0.0054**	0.0562
PTEN	0.0981	0.0994	0.4455
NF1	0.5083	0.7777	**0.0406**
EGFR	0.6198	0.5759	0.3122
ERBB2	--	--	--
RB1	**0.0425**	**0.0395**	0.2658
PIK3R1	0.3855	0.4448	1.0000
PIK3CA	0.7452	1.0000	1.0000
IDH1	0.7071	1.0000	0.3522

Lymphocytes are Enriched in the Mesenchymal Subtype

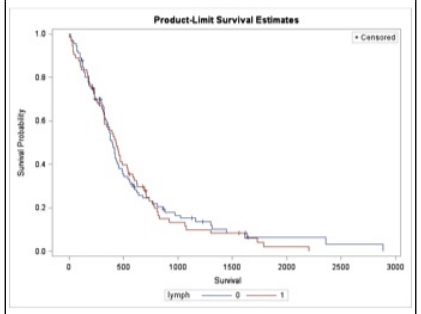
Verhaak Classification	Lymphocytes 0	1+	2+	Total
Classical	31	10	1	42
Mesenchymal	27	17	**12**	56
Neural	13	9	2	24
Proneural	19	18	2	39



Proneural, Neural, Classical and Mesenchymal subtypes

Lymphocytes were enriched in the mesenchymal transcriptional subtype ($p<0.05$). 71% of cases classified as having abundant (2+) lymphocytes were in the mesenchymal subtype.

Effect of Lymphocytes on Survival



Lymphocytes were not associated with prolonged survival

Conclusions

Tumor-infiltrating lymphocytes may have biologic and clinical significance in GBM. We found that lymphocytes were strongly correlated with the mesenchymal transcriptional subtype; with mutations in NF1, TP53 and RB1; and with histologic subtypes characterized by mutations in TP53, RB1 and NF1. Immunogenic mechanisms underlying these molecular associations remain to be further explored.

Learning Objectives

By the conclusion of this session, participants should be able to: 1) describe the significance of tumor-infiltrating lymphocytes in human neoplasms and 2) identify the molecular correlates of lymphocytes in glioblastoma.

References

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Supported in part by PHS Grant (UL RR025008, KL2 RR025009, or TL1 RR025010) from the Clinical and Translational Science Award program, National Institutes of Health, National Center for Research Resources