ScienceDirect

Cancer Cell

Available online 2 January 2025

In Press, Corrected Proof What's this?

Article

Infiltrating plasma cells maintain glioblastoma stem cells through IgG-Tumor binding

Jiancheng Gao [1 2 3 23], Danling Gu [1 3 4 23], Kailin Yang [5 23], Junxia Zhang [2 3 23], Qiankun Lin [1 3 23], Wei Yuan [6 23], Xu Zhu [7 23], Deobrat Dixit [8], Ryan C. Gimple [9], Hao You [1 3], Qian Zhang [1 3], Zhumei Shi [2], Xiao Fan [2 3], Qiulian Wu [8], Chenfei Lu [1 2 3], Zhangchun Cheng [2 3], Daqi Li [1 3], Linjie Zhao [8], Bin Xue [1], Zhu Zhu [10]...Xiuxing Wang [1 2 3 4 22 24]

Show more

Share Cite

https://doi.org/10.1016/j.ccell.2024.12.006

Get rights and content

Referred to by Plasma cell and cancer stem cell crosstalk in glioblastoma
Cancer Cell, Available online 2 January 2025, Pages
Elijah Kirschstein, Andrew J. Gunderson

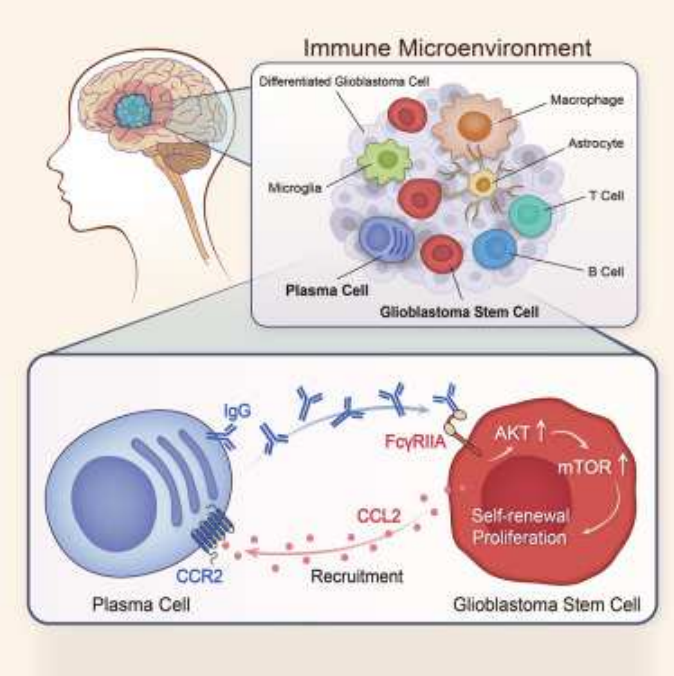
Highlights

- Plasma cells (PCs) are enriched in glioblastoma and associated with poor prognosis
- PCs promote glioblastoma stem cells growth through the IgG-FcγRIIA-AKT-mTOR axis
- Glioblastoma-infiltrating PCs are recruited to GSC niches via CCL2-CCR2 signaling
- Blocking PC-mediated stimulation of GSC represents a promising therapeutic strategy

Summary

Glioblastoma is a highly aggressive primary brain tumor with glioblastoma stem cells (GSCs) enforcing the intra-tumoral hierarchy. Plasma cells (PCs) are critical effectors of the B-lineage immune system, but their roles in glioblastoma remain largely unexplored. Here, we leverage single-cell RNA and B cell receptor sequencing of tumor-infiltrating B-lineage cells and reveal that PCs are aberrantly enriched in the glioblastoma-infiltrating B-lineage population, experience low level of somatic hypermutation, and are associated with poor prognosis. PCs secrete immunoglobulin G (IgG), which stimulates GSC proliferation via the IgG-FcγRIIA-AKT-mTOR axis. Disruption of IgG-FcγRIIA paracrine communication inhibits GSC proliferation and self-renewal. Glioblastoma-infiltrating PCs are recruited to GSC niches via CCL2-CCR2 chemokine program. GSCs further derive pro-proliferative signals from broadly utilized monoclonal antibody-based immune checkpoint inhibitors via FcγRIIA signaling. Our data generate an atlas of B-lineage cells in glioblastoma with a framework for combinatorial targeting of both tumor cell-intrinsic and microenvironmental dependencies.

Graphical abstract



Download: Download high-res image (229KB)

Download: Download full-size image

Introduction

Glioblastoma, the most common primary tumor of the central nervous system (CNS), remain uniformly aggressive and lethal, with a median survival of less than 2 years.[1,2,3,4] Glioblastoma stem cells (GSCs) possess the fundamental stem cell properties including self-renewal, multi-potency, and tumor maintenance, and they share other characteristics with normal neural stem

cells (NSCs).[5,6] Although they comprise a small fraction of total tumor cells, GSCs have been demonstrated to promote tumor angiogenesis, brain invasion, and immune evasion in glioblastoma.[7,8,9,10] Mechanisms underlying the interactions between normal tissue stem cells and their respective microenvironments within the stem cell niche have been documented[10]; however, the precise molecular interactions between GSCs and various stromal components in the tumor microenvironment (TME) remains to be explored.

GSCs live in a niche that consists of astrocytes, microglia, endothelial cells, tumor-associated macrophages (TAMs), and Tcells.[11,12,13] Prior studies have unveiled the multifaceted roles of TAMs and Tcells in the brain TME,[12,14,15,16] with B cells believed to play a primarily immunosuppressive role[17,18,19,20,21,22]; however, the frequency and functional roles of plasma cells (PCs) in the brain TME are underexplored. B cells and the immunoglobulin (Ig)-secreting PCs have a significant role in the immune system, primarily through empowering the humoral component of adaptive immunity.[23] In the tumor immune microenvironment, B cells and PCs can support anti-tumoral immune responses through antibody-dependent cell cytotoxicity (ADCC), phagocytosis of tumor cells, and presentation of tumor-derived antigens to Tcells.[24,25] In addition, B-lineage cells promote tumor growth through releasing immunosuppressive cytokines, producing antibodies that form immune complexes, and eventually present immunosuppressive phenotypes in myeloid cells.[26,27]

The roles of tumor-infiltrating B cells and PCs, and thus the prognostic and predictive significance of immunoglobulin repertoires, differ considerably depending on the stage and origin of the tumor.[28,29,30] Previous studies presented that the B cell signatures are significantly associated with improved survival in breast cancer patients,[31] and the presence of B cells and PCs with highsomatic hypermutation (SHM) promote antibody reactivity against tumor in head and neck cancer,[32] and high-grade serous ovarian carcinoma.[33] Other studies reported that B cell-derived soluble metabolites were found to promote the colon carcinoma growth.[34] In addition, B cells and PCs in tumor region predict the therapeutic responses to immune checkpoint inhibitors in non-small cell lung cancer and renal cell carcinoma.[35,36] However, the relationship between B-lineage cells, especially PCs, and GSCs remains unclear and warrants further exploration. In this study, we determined single-cell RNA and PC-focused single-cell B cell receptor (BCR) profile of tumor-infiltrating B-lineage cells in primary glioblastoma specimens and characterized thefunctional relationship between tumor-infiltrating PCs and GSCs.

Section snippets

PCs are aberrantly enriched among tumor-infiltrating B-lineage cells in glioblastoma

To characterize the landscape of B-lineage cells in glioblastoma, we first performed immunofluorescence on primary glioblastoma specimens and confirmed the presence of infiltrating CD45 and CD19 double-positive B-lineage cells, which are molecular markers for

immune cells and B-lineage cells, respectively (FigureS1A). Then, we interrogated two datasets of glioblastoma that were not selected for specific cell types, a single-cell RNA sequencing (scRNA-seq) of 16 fresh samples (dataset A) and a …

Discussion

The cellular hierarchy of glioblastomas is generated and maintained by GSCs, which promote tumor growth, therapeutic resistance, invasion into normal brain, immune escape, and angiogenesis.[5,7,10,13] Although, high levels of tumor-infiltrating Bcells have been observed in human cancers,[26,32,34,35] the roles of tumor-infiltrating PCs are underappreciated. In this study, we leveraged single-cell analyses from patient tumors, and found that glioblastomas contain several subtypes of developmentally …

Lead contact

Further information and requests should be directed to and will be fulfilled by the lead contact, Dr. Xiuxing Wang (drxiuxingwang@163.com ↗). …

Materials availability

This study did not generate new unique reagents. …

Data and code availability

The data reported in this paper have been deposited in the PRJCA016872, in the Genome Sequence Archive in National Genomics Data Center China National Center, China National Center for Bioinformation,Beijing Institute of Genomics, Chinese Academy of Sciences.[100,101] The raw data of sequencing are publicly …

Acknowledgments

We thank the Nanjing Medical University Analysis Center for help with FACS; animal core facility of Nanjing Medical University for help with animal experiments; J. Zhang and F. Wang for generously providing the access to healthy donor peripheral blood scRNA-seq and scBCR-seq data; H. Kadara and L. Wang for kindly providing the access to lung adenocarcinoma-infiltrating B-lineage cell scRNA-seq and scBCR-seq data; X. Mai and Y. Zhang for kindly providing the access to breast cancer-infiltrating …

Author contributions

Conceptualization, N. Zhang, J.N.R., Y.Y., and Xiuxing Wang; methodology, J.G., D.G., W.G., Y. Lu, D.H., S.Y., Y.C., Xiaoming Wang, Q. Wang, S.C.M., Z.H., C. Li., M.D.T., and Y. Li; software, J.G., K.Y., Q.L., and X.F.; validation, J.G., D.G., and Q.L.; formal analysis, J.G., D.G., and Q.L.; investigation, J.G.,

D.G., Q.L., W.Y., X.Z., H. You, Q.Z., Z.S., Q. Wu, C. Lu, Z.C., D.L., L.Z., Zhu Zhu, Zhe Zhu, H. Yang, N. Zhao, J.M., and S.A.; resources, J.Z., N. Zhang, J.N.R., Y.Y., Xiuxing Wang., …

Declaration of interests

The authors declare no competing interests. …

Key resources table

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Antibodies		
Human TruStain FcX™ (Fc Receptor Blocking Solution)	BioLegend	Cat# 422302; RRID: AB_2818986 ↗
FITC Mouse Anti-Human CD45	BD Biosciences	Cat# 555482; RRID: AB_395874 ↗
PE Mouse Anti-Human CD19	BD Biosciences	Cat# 555413; RRID: AB_395813 ↗
CD45 Antibody, anti-mouse, REAfinity™	Miltenyi Biotec	Cat# 130-110-803; RRID: AB_2658224 ↗
CD45 Monoclonal Antibody (2D1), APC-Cyanine7	Thermo Fisher Scientific	Cat# MA5-38731; RRID: AB_2898643 ↗
BUV395 Mouse Anti-Human CD3	BD Biosciences	Cat#

…

…

…

Recommended articles

References (118)

A.G. Alvarado *et al.*
Glioblastoma Cancer Stem Cells Evade Innate Immune Suppression of Self-Renewal through Reduced TLR4 Expression
Cell Stem Cell (2017)

B.C. Prager *et al.*
Cancer Stem Cells: The Architects of the Tumor Ecosystem
Cell Stem Cell (2019)

N.D. Mathewson *et al.*
Inhibitory CD161 receptor identified in glioma-infiltrating Tcells by single-cell analysis
Cell (2021)

D. Mrdjen *et al.*
High-Dimensional Single-Cell Mapping of Central Nervous System Immune Cells Reveals Distinct Myeloid Subsets in Health, Aging, and Disease
Immunity (2018)

J.G. Cyster *et al.*
B Cell Responses: Cell Interaction Dynamics and Decisions
Cell (2019)

R.D. Mazor *et al.*
Tumor-reactive antibodies evolve from non-binding and autoreactive precursors
Cell (2022)

M. Meylan *et al.*
Tertiary lymphoid structures generate and propagate anti-tumor antibody-producing plasma cells in renal cell cancer
Immunity (2022)

L.B. Wang *et al.*
Proteogenomic and metabolomic characterization of human glioblastoma
Cancer Cell (2021)

C.A. Herring *et al.*
Human prefrontal cortex gene regulatory dynamics from gestation to adulthood at single-cell resolution
Cell (2022)

Y. Lu *et al.*
Complement Signals Determine Opposite Effects of B Cells in Chemotherapy-Induced Immunity
Cell (2020)

View more references

Cited by (0)

23 These authors contributed equally

24 Lead contact

View full text