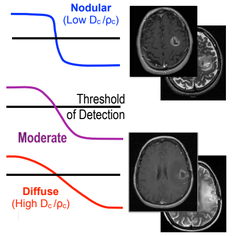
Leveraging Transcriptome Sequencing and Mathematical Modeling to Investigate Glioblastoma-Macrophage Interactions

Javier C. Urcuyo[1], Andrea Hawkins-Daarud[1], Susan Christine Massey[1], Jeffrey N. Bruce[2], Peter D. Canoll[3], Nhan L. Tran[4], Leland S. Hu[5], Kristin R. Swanson, Ph.D.[1]

[1]Precision Neurotherapeutics Innovation Program, Division of Neurologic Surgery, Mayo Clinic. [2]Department of Neurological Surgery, Columbia University. [3]Department of Pathology and Cell Biology, Columbia University. [4]Department of Cancer Research, Mayo Clinic. [5]Department of Radiology, Mayo Clinic.

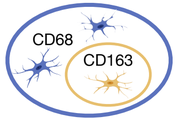
Background

- Glioblastoma (GBM) is a heterogeneous, diffusely-infiltrating brain tumor, with a poor overall survival of only 14.6 months [1].
- Due to its infiltrative nature, only a portion of the tumor population is detectable on MR imaging.
- Many novel treatments, including immunotherapies, have had limited success in improving survival [2].
- Innate immune response includes recruitment of resident microglia and peripheral macrophages.
- However, both types of immune cells have been shown to exhibit a phenotype that promotes a microenvironment permissive of tumor growth [3].

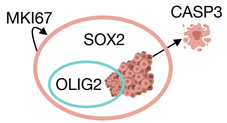


Methodology

- RNA sequencing was performed on tissue to gain a better understanding of the interacting populations within the tumor, focusing on genetic markers representative of tumor and microglia/macrophage dynamics.
- Biopsies were collected from contrast-enhancing (n=39) and non-enhancing (n=36) regions from 27 patients at Columbia University.
- Findings were validated using available RNA-Seq data from TCGA, although information regarding sample location was not available in 166 patients, yielding 172 biopsies.



Glioma-Associated Microglia/Macrophages



Tumor

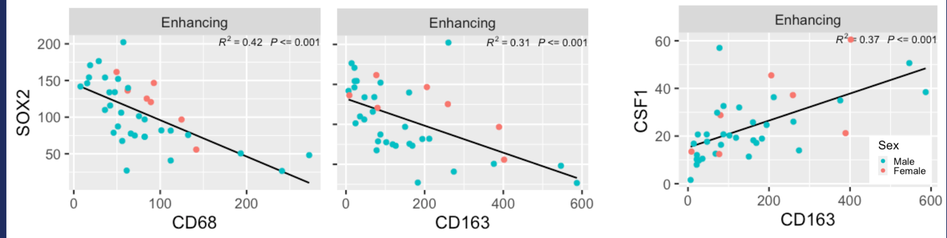
Investigation: Correlations between RNA-Seq Markers

Although CD68 is a general marker of glioma-associated microglia/macrophages (GAMMs), CD163 is a marker more readily associated with tumor-permissive GAMMs [4]. Additionally, single-cell sequencing demonstrated that SOX2 is widely-expressed in glioma cells [5].

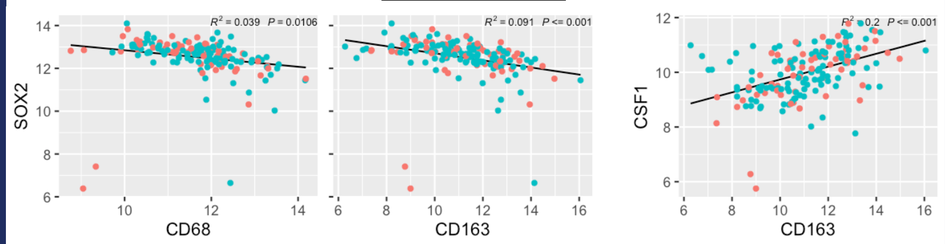
Upon comparing various tumoral and microglial markers, both aforementioned GAMM markers (CD68, CD163) are significantly negatively correlated with the tumor marker SOX2. Conventionally, permissive GAMMs are thought to promote tumor growth, but these findings suggest that the tumor may not benefit from the presence of GAMMs.

We also found that CD163 is significantly positively correlated with CSF-1. Of therapeutic interest, CSF-1 may be a marker for the conversion from suppressive to permissive GAMMs.

Columbia University

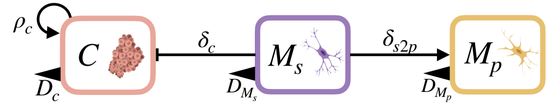


Validation: TCGA



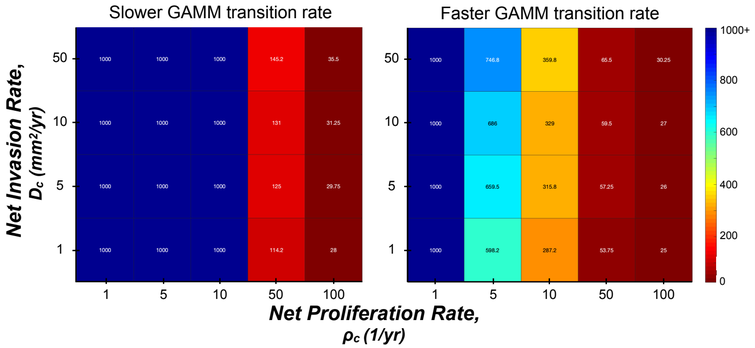
Investigation: Mathematical Modeling

To further capture the underlying dynamics of GBM-GAMM interactions, we extended the well-studied Proliferation-Invasion model of glioma growth [6] to include both suppressive and permissive GAMM populations.



Where C represents tumor cells, M_s represents suppressive GAMMs, and M_p represents permissive GAMMs. Each population diffuses/invades at respective rates $D_{\{C,Ms,Mp\}}$. Additionally, tumor cells proliferate at the rate ρ_C. As GAMMs and tumor cells compete for space, the tumor proliferation rate is limited in the presence of GAMMs. Suppressive GAMMs aid in tumor death at the rate δ_C, but may also transition to permissive GAMMs at the rate δ_{s2p}.

Time for Tumor to Grow 100 Times its Size



We use the model to explore the implications of varying the transition rate between tumor suppressive and permissive GAMMs (δ_{s2p}). We see that a faster transition rate results in quicker tumor growth when compared to a slower transition rate. This finding suggests that targeting the transition between suppressive and permissive GAMMs might have therapeutic efficacy in slowing tumor growth.

Future Work

- Identify candidate markers of the transition between suppressive and permissive GAMMs
- Simulate interventions that best target GAMMs to identify novel vulnerabilities to hamper tumor progression

References

1. Stupp, et al. *New England Journal Medicine*, 352: 987-996, 2005.
2. Reardon, et al. *NeuroOncology*, 16(11): 1441-1458, 2014.
3. Roesch, et al. *Int. J. Molecular Science*, 19(2): 436, 2018.
4. Buechler, et al. *J. Leukoc. Biol.*, 67(1): 97-103, 2000.
5. Yuan, et al. *Genome Med.*, 10(1), 57, 2018.
6. Swanson, et al. *J. Neurol. Sci.*, 216(1): 1-10, 2003.

Acknowledgments

This material is based upon work supported by the Cancer Systems Biology Consortium of the National Institute of Health under a diversity supplement associated with Grant No. U01CA220378. Special thanks to Lee Curtin and Kamila Bond for their input on this work.

For more information: www.mathematicalneurooncology.org