Elucidating the Role of Microbiome in Low- and High-Grade Glioma

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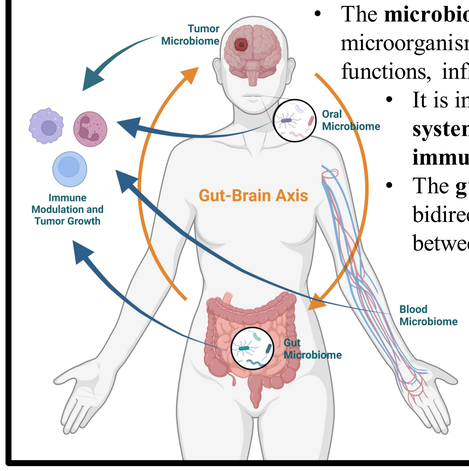
BACKGROUND AND PURPOSE

Glioma: a type of central nervous syetem tumor that originates from glial cells, classified into grades I - IV

- Low-Grade Glioma — IDH mutant
- High-Grade Glioma — IDH wild type

- **Glioblastoma** (stage IV glioma) is the most prevalent malignant adult brain tumor, characterized with a poor prognosis despite maximal therapy.
- **Immunotherapy**, specifically immune checkpoint blockade, has been **effective in other solid malignancies**, but it has demonstrated **limited success against glioblastoma**, likely due to its **immunosuppressive tumor microenvironment.**[1]



- The **microbiome** consists of microorganisms with various properties and functions, influencing human physiology.
  - It is involved in **the immune system** and **tumor progression and immunity** in various tumors.[2]
  - The **gut-brain axis** is the bidirectional communication between the brain and gut.[3]

However, the role of the microbiome and microbiota-driven immune modulation in glioma is still largely unknown.

OBJECTIVES

- Determine the immunomodulatory role of the microbiome in the brain
- Determine the association of the gut microbiome with tumor progression in glioblastoma patients

METHODS

Pre-Clinical

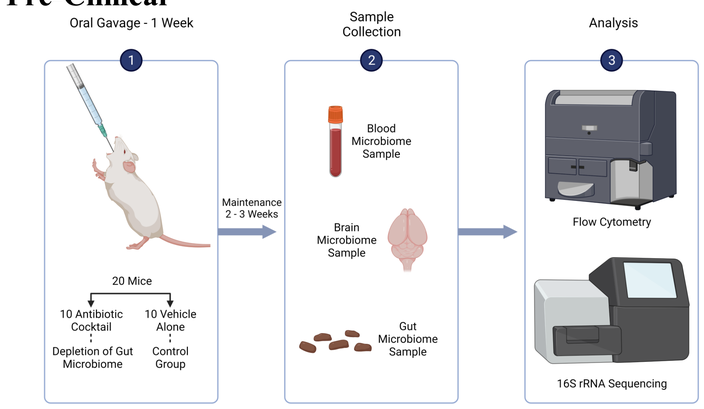


Figure 1. Schematic demonstrating the experimental design of pre-clinical studies. The in vivo models consist of control mice treated with vehicle alone and mice treated with a cocktail of non-absorbable broad-spectrum antibiotics to deplete the gut microbiome. The brains were collected and analyzed to determine immune profiles.

Clinical

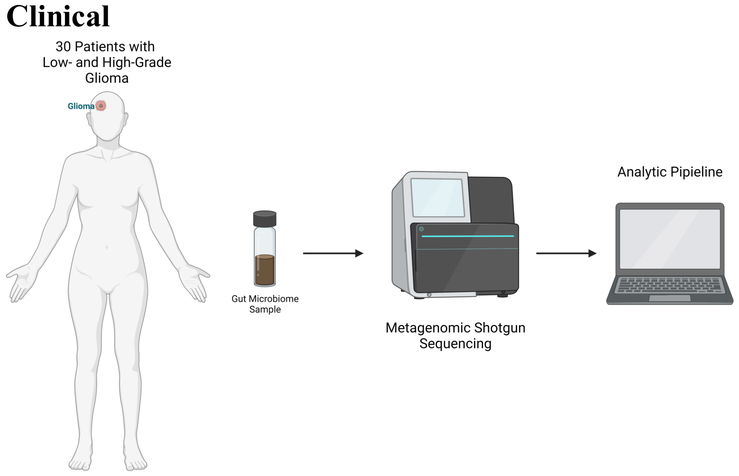


Figure 2. Schematic demonstrating the experimental design of clinical studies. Microbiome samples from 30 patients with low- and high-grade glioma at the time of surgical resection of brain tumors were collected and analyzed in order to determine the association of microbial signatures with low- and high-grade glioma and tumor progression metrics.

RESULTS

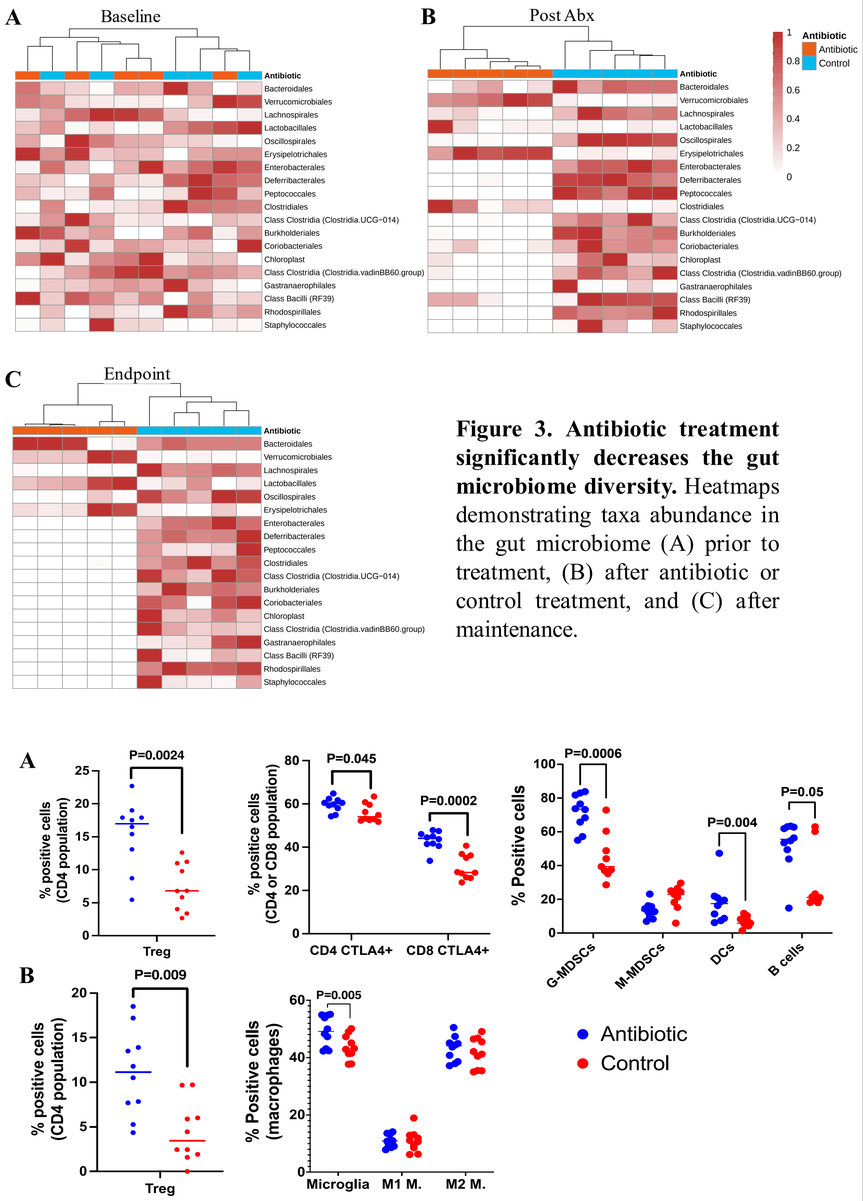


Figure 3. Antibiotic treatment significantly decreases the gut microbiome diversity. Heatmaps demonstrating taxa abundance in the gut microbiome (A) prior to treatment, (B) after antibiotic or control treatment, and (C) after maintenance.

Figure 4. Depletion of the gut microbiome in non-tumor-bearing mice induced an immunosuppressive environment in the brain. Column scatter plot demonstrating immune profiles in the (A) blood and (B) brain microbiomes using flow cytometry.

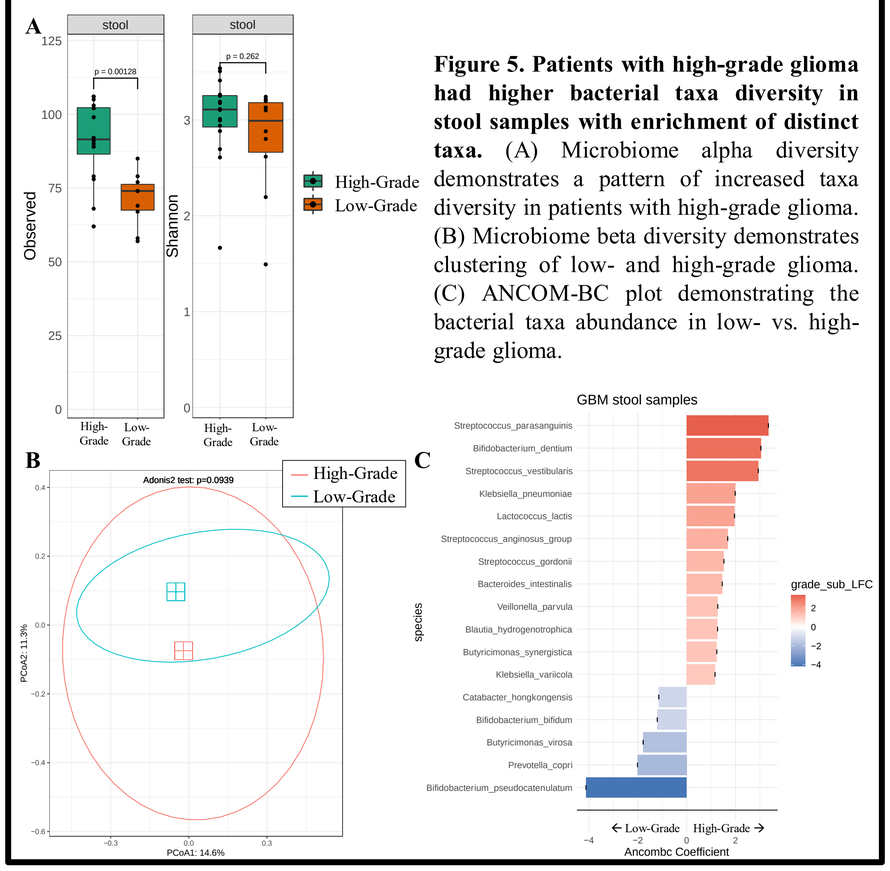


Figure 5. Patients with high-grade glioma had higher bacterial taxa diversity in stool samples with enrichment of distinct taxa. (A) Microbiome alpha diversity demonstrates a pattern of increased taxa diversity in patients with high-grade glioma. (B) Microbiome beta diversity demonstrates clustering of low- and high-grade glioma. (C) ANCOM-BC plot demonstrating the bacterial taxa abundance in low- vs. high-grade glioma.

RESULTS

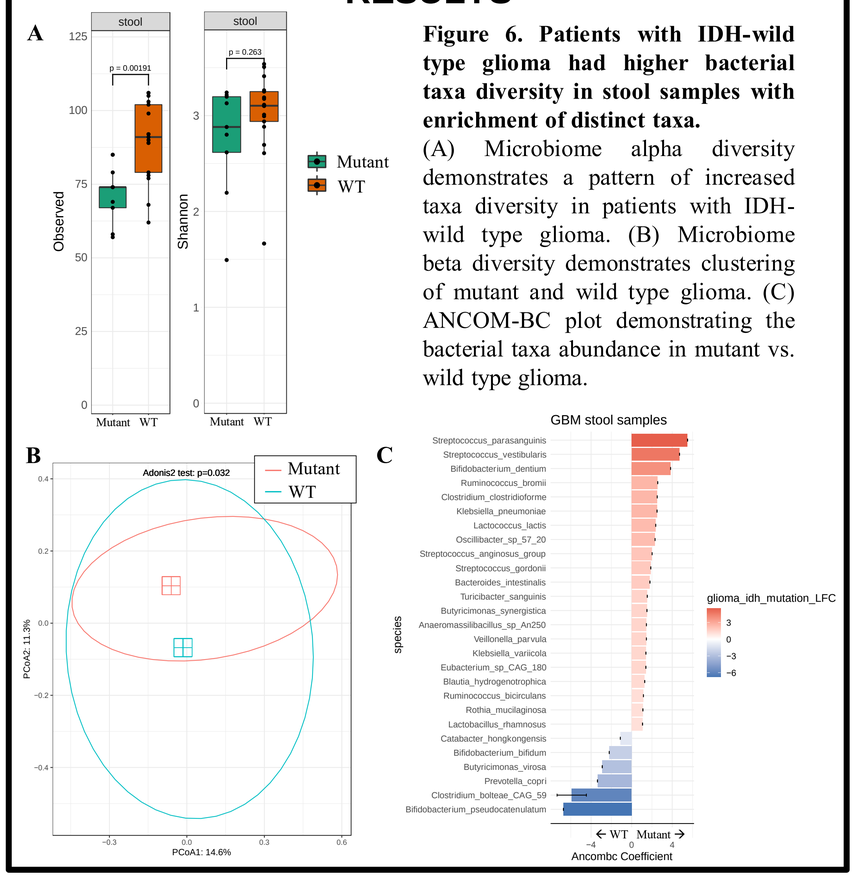


Figure 6. Patients with IDH-wild type glioma had higher bacterial taxa diversity in stool samples with enrichment of distinct taxa. (A) Microbiome alpha diversity demonstrates a pattern of increased taxa diversity in patients with IDH-wild type glioma. (B) Microbiome beta diversity demonstrates clustering of mutant and wild type glioma. (C) ANCOM-BC plot demonstrating the bacterial taxa abundance in mutant vs. wild type glioma.

CONCLUSIONS/FUTURE DIRECTIONS

- The absence of gut microbiota can modulate the regulation of T cell and microglia activity, inducing an immunosuppressive microenvironment in the brain.
- Enrichment of distinct microbial communities are associated with grade and IDH type of glioma.
- Next Steps: spatial transcriptomics to investigate the distribution of cells and microbes in the tumor microenvironment

SIGNIFICANCE

- This combination of clinical and pre-clinical studies **addresses the role of the gut microbiome in glioma** and uncovers novel mechanisms that lay the groundwork for the **development of novel early diagnostic, preventative, and therapeutic strategies** for glioma and improve immune-targeting therapies.
- **Identifying microbial signatures predictive of glioma development or of glioma progression to glioblastoma** can potentially be used for early detection.
- **Microbiome modulation is amenable to non-invasive measures**, so depending on the **microbial biomarkers** identified, **preventative, non-invasive measures** can target the relevant microbial communities to **improve patient outcomes**.

RESPONSIBLE CONDUCT OF RESEARCH

The MD Anderson PI submitted a research protocol and obtained research approval. Ethical needs and protections for animal welfare and safe laboratory practices were considered and approved by the IACUC. Protocol was strictly followed for data acquisition, management, ownership, and sharing to ensure patient privacy.

REFERENCES

1. Lim et al., *Nature Reviews Clinical Oncology* 2018
2. Helmink et al., *Nature Medicine* 2019
3. Morais et al., *Nature Reviews Microbiology* 2021

ACKNOWLEDGEMENTS

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Glioblastoma Moon Shot® Program

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