The role of different microbiota in metastatic brain tumors

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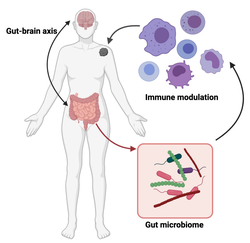
ABSTRACT

Background: Metastatic brain tumors are associated with significant morbidity and mortality. The current limited understanding of the mechanisms underlying brain metastasis has hindered the development of efficient diagnostics and therapeutics for this disease. The microbiota has emerged as a novel hallmark of cancer, with a prominent role in tumorigenesis, tumor immunity, and response to treatment. However, the role of different microbial communities in tumor metastasis, and in particular brain metastasis, is poorly understood. We hypothesize that distinct microbial communities can alter the immune microenvironment in the brain and affect brain metastasis development.
Methods: To evaluate the role of different microbial communities in brain metastasis, matched stool, saliva, tumor, and plasma samples were collected prospectively from patients with metastatic brain tumors who underwent surgical tumor resection at the University of Texas MD Anderson Cancer Center. Stool and saliva samples were collected using the OMNIgene microbiome collection and stabilization kits (DNAgenotek, Kit # OM-200 and OM-505, respectively). Tumor samples were flash frozen in sterile conditions. Stool and saliva samples from 30 patients and tumor and plasma from 15 patients were sequenced via metagenomic shotgun and 16S rRNA sequencing, respectively. Microbiome profiling was conducted through established computational pipelines reported previously by our group. To further explore the mechanistic role of the gut microbiota in brain metastasis, we depleted gut microbiota in conventionally raised mice using a broad-spectrum non-absorbable antibiotic regimen. Melanoma tumor cells were subsequently injected intracranially to evaluate the effect of gut microbiota depletion and associated immune changes on tumor growth. Tumor growth was measured through in vivo bioluminescent imaging and histology. Peripheral and tumor immune profiling was conducted through flow cytometry and immunohistochemistry.
Results: In all types of microbiota evaluated in this study, distinct signatures were identified to be associated with brain metastasis compared to other types of brain tumors. Interestingly, we demonstrated an overlap between the tumor microbiome and the oral microbiome but not with the gut microbiome. These findings suggest a direct contribution of the oral microbiome and the potential indirect contribution of the gut microbiome to the development of brain metastasis. Our mechanistic studies on the role of gut microbiota in brain metastasis demonstrated that depletion of the gut microbiota in mice decreased tumor growth in the brain. Evaluation of the peripheral and tumor immune profiles suggested the underlying mechanisms to involve alterations in the circulating cytokine profiles and an increase in anti-tumor T cell activity.
Conclusion: Our clinical studies suggest the association of distinct microbial communities with brain metastasis. Our pre-clinical findings demonstrate that the absence of gut microbiota can modulate the regulation of T cell activity to induce an anti-tumor response in the brain. Further studies, currently in progress, will determine the individual and collective role of different microbial communities in the development of brain metastasis.

BACKGROUND



- Gut and oral microbiome contributes to different aspects of tumor progression[1,2]; however, their role in primary and metastatic brain tumors remains unknown.
- The gut-brain axis is the bidirectional communication between the gut microbiota and the brain and contributes to a variety of neurological disorders [3].

We hypothesize that distinct gut and oral microbial signatures contribute to the development of metastatic brain tumors.

METHODS

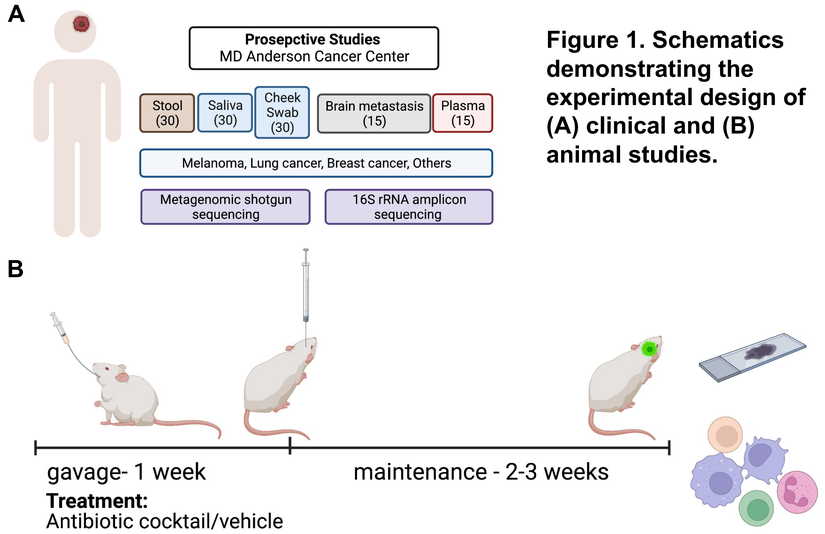


Figure 1. Schematics demonstrating the experimental design of (A) clinical and (B) animal studies.

RESULTS

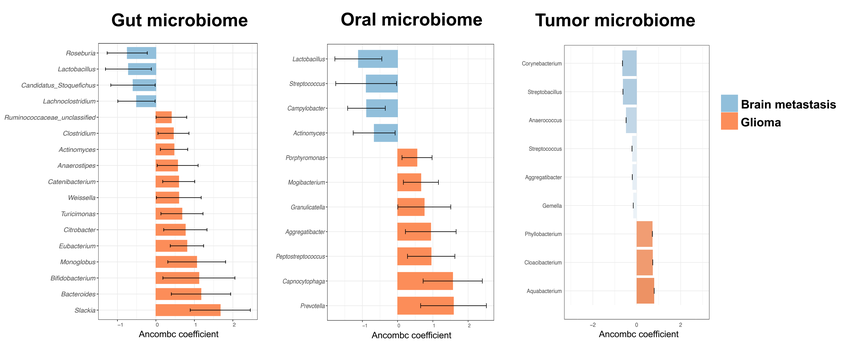


Figure 2. Distinct microbial signatures in the gut, oral, and tumor microbiome are enriched in brain metastasis compared to primary brain tumors. Analysis of Compositions of Microbiomes with Bias Correction (ANCOM-BC) demonstrating enrichment of taxa in samples from brain metastasis patients (blue) and primary brain tumors (orange).

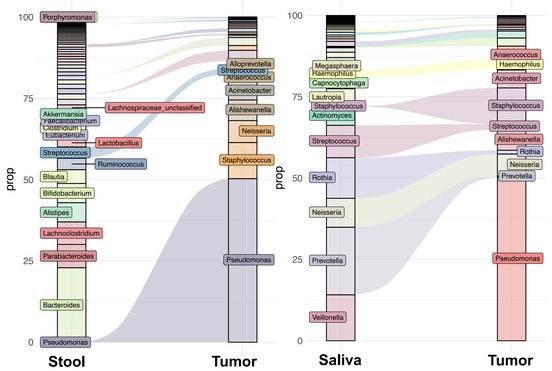
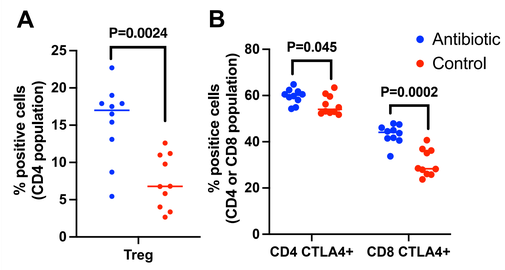
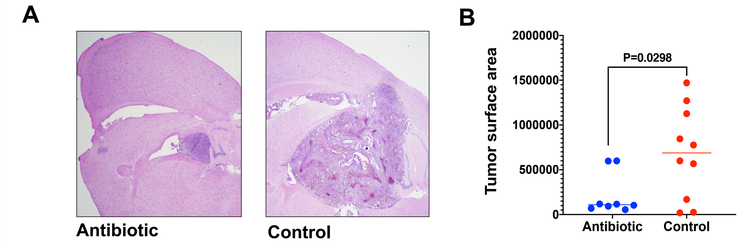


Figure 3. Tumor microbiome overlaps with oral microbiome, suggesting the possibility of direct contribution. Alluvial plots demonstrating the overlap between bacterial taxa in the tumor microbiome and gut (left) or oral (right) microbiome.

RESULTS





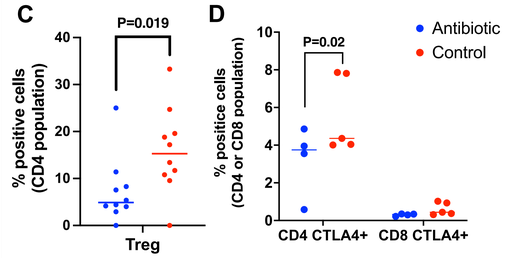


Figure 4. Antibiotic treatment was associated with alterations in the peripheral immune profile in non-tumor bearing mice. Gut microbiome depletion increased the circulating Treg population (A) and the CTLA4+ CD4 and CD8 populations (B).

Figure 5. Depletion of the gut microbiome was associated with a decrease on melanoma tumor growth in the brain. Tumor size at the site of injection was evaluated by histology (A) and quantified using ImageJ (B). Peripheral immune profiling demonstrate a decrease in Tregs (C) and the CTLA4+ CD4 cells (D).

CONCLUSIONS

- We identified distinct gut, oral, and tumor bacterial signatures that were enriched in brain metastasis patients compared to primary tumors.
- Our findings suggest a direct contribution of the oral microbiome and the potential indirect contribution of the gut microbiome to the development of brain metastasis.
- Our pre-clinical findings demonstrate that the absence of gut microbiota can regulate T cell activity to induce an anti-tumor response in the brain.

REFERENCES

1. Gopalakrishnan et al., *Science* 2018
2. Helmink et al., *Nature Medicine* 2019
3. Morais et al., *Nature Reviews microbiology* 2021

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