News Release

Title

Newly Established Experimental Model for Meningioma Research
: Patient-derived meningioma organoid model for unraveling tumor biology leads to new therapeutic strategies

Key Points

- Meningioma is the most common primary tumor of the central nervous system (CNS). Tumor removal is the first-line treatment followed by adjuvant radiotherapies for residual lesions or malignant meningiomas cases. Any targeted therapy has not been identified yet because of the limited number of representative experimental models for meningioma.
- We developed a new method to establish meningioma organoid models from patient-derived tumor tissues, which enabled us to perform *in vitro* experiments. Meningioma organoid models recapitulated histological features and molecular profiles of its corresponding parental tumor.
- *In vitro* studies using this experimental model revealed that *forkheadbox M1* (*FOXM1*) contributed to the tumor growth. Additionally, FOXM1 inhibitor combined with radiation therapy suppressed the tumor proliferation of meningioma.

Summary

Recent comprehensive studies have revealed several molecular alterations that are frequently found in meningiomas. However, effective treatment reagents targeting specific molecular alterations have not yet been identified because of the limited number of representative research models of meningiomas. In this study, we established 18 organoid models comprising of two malignant meningioma cells (HKBMM and IOMM-Lee), 10 benign meningiomas, four malignant meningiomas, and two solitary fibrous tumors (SFTs). The organoids exhibited consistent histological features and molecular profiles similar to those of the parental tumors. Using a public database, we identified that upregulated *forkhead box M1 (FOXM1)* was correlated with increased tumor proliferation. Overexpression of *FOXM1* in benign meningioma organoids increased organoid proliferation; depletion of *FOXM1* in malignant organoids decreased proliferation. Additionally, thiostrepton, a FOXM1 inhibitor combined with radiation therapy, significantly inhibited proliferation of malignant meningioma organoid models. An organoid model for meningioma enabled us to elucidate the tumor biology of meningioma along with potent treatment targets for meningioma.

Research Background

Meningioma is the most common primary tumor of the CNS and is classified by the world Health Organization as Grade I-III according to its histopathological features. Although 80% of meningiomas are benign tumors (Grade I) and most Grade I meningioma cases are favorably

managed by surgical tumor removal, some cases of benign meningioma located at technically challenging locations for extended total removal or malignant meningiomas exhibited higher recurrence rate, despite frequent use of adjuvant radiation therapy. Recent comprehensive genetic analysis revealed several alterations frequently found in meningioma tissues, however, effective treatment reagents for recurrent meningiomas have not been identified. This is partly because there are a limited number of established experimental materials, such as meningioma cell lines or animal models to perform functional analyses of these genetic alterations. Recently, organoid culture technologies have been developed that represent phenotypic and molecular features in various cancers. The efficiency of the organoid establishment has been reported to be higher than the tumor cell lines or patient-derived xenograft models. In this study, using patient-derived tumor tissues, we established meningioma organoid models that could be a reliable platform for basic and clinical research on meningiomas.

Research Results

In this study, we established 16 organoid models including 14 meningiomas, and two SFTs cases, using 16 patient-derived tumor tissues, with a 100% success rate. Established organoids exhibited morphological findings similar to those of parental tumor tissues confirmed by HE staining. Immunohistochemistry revealed that these organoid models exhibited molecular features similar to those of each parental tumor tissues (Figure 1).

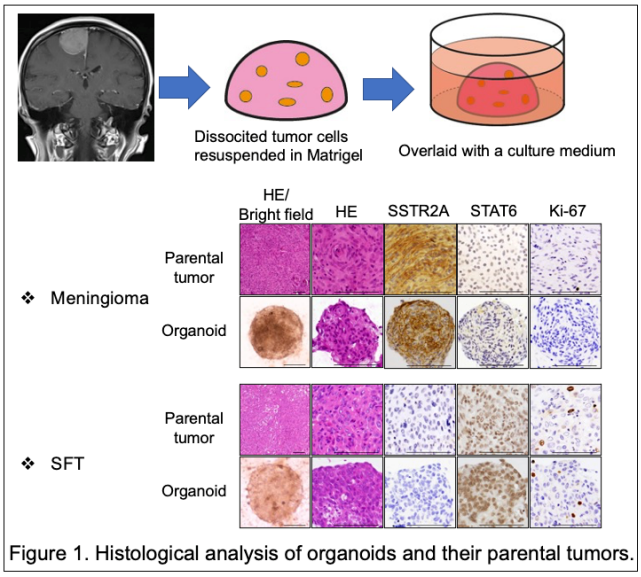

Figure 1. Histological analysis of organoids and their parental tumors.

Genetic alteration analyses (whole-exome sequencing), gene expression analyses (RNA-Seq) and DNA methylation analyses demonstrated that organoid models exhibited molecular profiling similar to those of their parental tumors (Figure 2). All these data indicated that

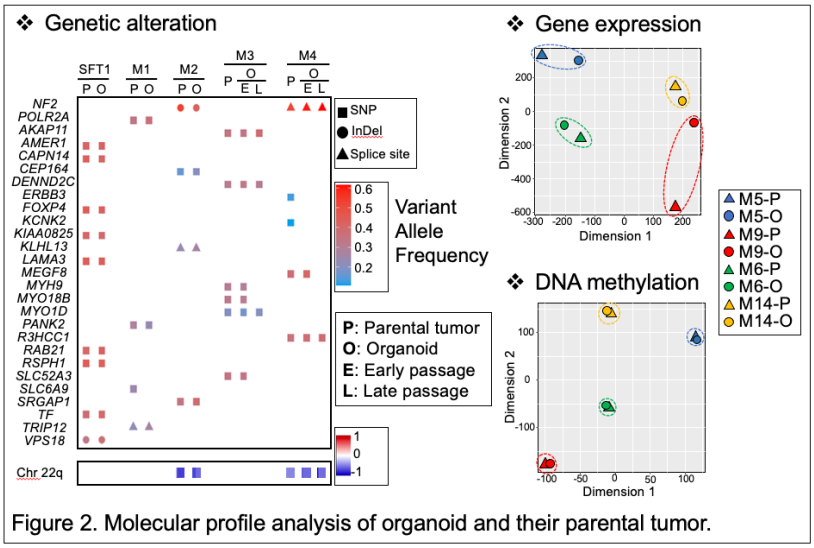

Figure 2. Molecular profile analysis of organoid and their parental tumor.

the established meningioma organoids maintained the histological and molecular features of corresponding parental tumors.

The analysis of published gene expression data for each grade of meningiomas revealed that aberrantly upregulated *FOXM1* was the most strongly correlated with high proliferation index of meningioma. Using the organoid models, overexpression of the *FOXM1* gene increased Grade I meningioma organoid proliferation. In contrast, knockdown of *FOXM1* in malignant meningioma organoids inhibited organoid growth. Thiostrepton, a FOXM1 inhibitor, combined with radiation therapy significantly inhibited the proliferation of malignant meningioma organoid models. *In vitro* experiments using the organoid model of benign or malignant meningioma demonstrated that aberrantly upregulated *FOXM1* might be a potent treatment target.

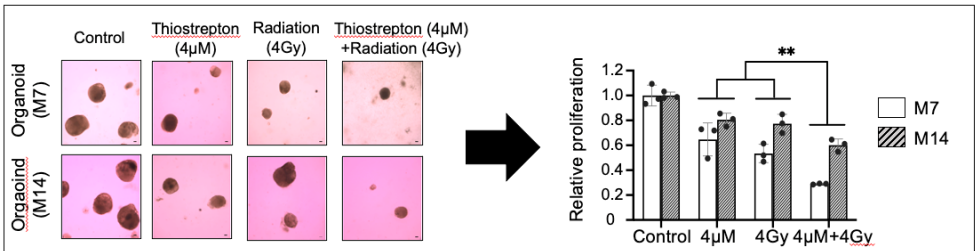

Figure 3. Radiation therapy and/or treatment with thiostrepton for meningioma organoid models.

Research Summary and Future Perspective

We have developed a culture method that can efficiently establish organoid models from patient-derived tumor tissues. As those organoid models exhibited consistent histological and molecular features with those of parental tumors, these organoid models could be a novel representative research model of meningioma. *In vitro* experiments using this model suggested that an upregulation or knockdown of *FOXM1* expression contributed to the meningioma proliferation. Additionally, FOXM1 inhibitor suppressed the tumor growth. Concerning all these results, further examination using meningioma organoid model could unravel the mechanisms underlying the tumor growth suppression by FOXM1 inhibitor.

Publication

Title: Newly Established Patient-derived Organoid Model of Intracranial Meningioma

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