TUMOR BIOLOGY/MODELS (TB)

TB-02

COMPREHENSIVE ANALYSIS OF EXPANDABLE BENIGN PITUITARY ADENOMAS WITHOUT GENETIC MANIPULATIONS

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BACKGROUND: Since most pituitary adenomas are benign, there is no model of pituitary adenomas that can be continuously cultured without genetic manipulation. In this study, we analyzed the genetic characteristics of the established cell lines by continuous culture of benign pituitary adenomas without genetic manipulation. METHOD: The pituitary adenoma was continuously cultured by modifying the conditional reprogramming (CR) method, and the morphology was observed and fluorescent immunostaining (IF) was performed. In addition, genetic characteristics were comprehensively analyzed, differences from the surgical samples were analyzed by enrichment analysis using GSEA, and network analysis was performed using cytoscape based on the protein-protein interaction database. (Results) 1) Of the 14 cases of pituitary adenoma that had undergone primary culture (median MIB-1 labeling index 1.5%), 12 cases were capable of continuous culture for more than 2 months. (6 months or more: 5 cases) 2) After 2 weeks of culturing, the cell morphology changed dramatically. These cultured cells were positive for follicular cell marker s100, ectodermal nervous system markers Nestin, Notch1, and mesodermal marker Vimentin. In these cells, synaptophysin, which was strongly positive in the surgical specimen collected at the same time as the culture, disappeared. 3) Enrichment analysis revealed that gene expression such as epithelial mesenchymal transition(EMT), angiogenesis, IL6 signaling via NFkB, extracellular degradation, integrin cell surface interaction increased in cultured cells, and gene expression such as neurotransmitter including synaptophysin decreased significantly.(Conclusion) 1) The modified CR method allowed continuous culture of pituitary adenoma cells. 2) The cultured cells showed characteristic change of EMT, which was seen in invasive pituitary adenoma.

TB-03

NEWLY ESTABLISHED MENINGIOMA ORGANOID MODEL ELUCIDATED AN IMPORTANT ROLE OF *FOXM1* IN MENINGIOMA PROGRESSION

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Meningioma is the most frequently occurring intracranial neoplasms in adults. Tumor removal surgery and radiotherapy were the widely accepted standard treatment for meningioma. Most meningioma cases were cured by extended total removal. However, some tumors develop in locations less amenable to resection, resulting in tumor recurrence after incomplete tumor removal followed by radiotherapy. Although several comprehensive studies have revealed frequently found molecular alterations of meningiomas, effective treatment reagents targeting specific molecular alterations have not been identified yet because of limited number of representative research models such as tumor cell lines or animal models of meningiomas. Recently developed 3D culture technologies have led to the development of novel cancer models, termed organoid models, due to their quite high efficiency of establishment. In this study, we established primary organoid culture methods using malignant meningioma cell lines (e.g. HKBMM and IOMM-Lee) and patient-derived meningioma tissues. Using this novel method, we have been able to establish six organoid models (four WHO grade I meningiomas, one WHO grade III one and one solitary fibrous tumor (SFT)) using tumor tissues derived from six consecutive patients with 100% success rate. Histological analyses, whole exome sequencing and copy number analyses revealed that these organoids exhibited consistent histological features and molecular profiling with those of parental tumors. Using public database, we identified upregulated *FOXM1* was correlated with increased tumor proliferation. Over-expression of *FOXM1* in benign meningioma organoids increased organoid proliferation, while depletion of *FOXM1* in malignant ones decreased their proliferation. We revealed that novel organoid model for meningioma enable to shed light on the tumor biology of meningioma.

TB-06

ERIBULIN PROLONGS SURVIVAL IN AN ORTHOTOPIC XENOGRAFT MOUSE MODEL OF MALIGNANT MENINGIOMA

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Meningioma is the most common intracranial tumor, and its prognosis is typically favorable. However, patients of malignant meningioma (WHO grade III) most often experience recurrence, undergo multiple surgical treatments, and have poor prognosis. No effective therapy for malignant meningioma has been established yet. We recently reported an efficacy of eribulin (Haraven®) for glioblastoma. Eribulin is considered to target TERT, which is frequently mutated in its promoter. Since TERT promoter mutation is also found in malignant meningioma, this study aims at investigating the anti-tumor effect of eribulin against TERT promoter mutation-harboring human malignant meningioma cell lines in vitro and in vivo.

Two meningioma cell lines IOMM-Lee and HKBMM were used in this study. In the viability assay and the flow cytometry, eribulin strongly inhibited cell proliferation by cell cycle arrest. Apoptotic cell death in malignant meningioma cell lines was confirmed by vital dye assay and immunoblotting. Moreover, wound healing assay revealed the suppression of tumor cell migration after eribulin exposure. To assess the effect of eribulin in vivo, orthotopic xenograft mouse models of both malignant meningioma cell lines were constructed. The intraperitoneal administration of eribulin significantly prolonged the survival of meningioma cell lines implanted in the brain ($p<0.0001$). Furthermore, apoptosis was histologically observed in brain tumor tissue by immunohistochemistry.

Thus, this study suggests that eribulin is a potential therapeutic agent for treating malignant meningioma.

IMMUNOLOGY (IM)

IM-03

CD206 EXPRESSION IN PERIPHERAL BLOOD-DERIVED INDUCED-MICROGLIA-LIKE CELLS AS A SURROGATE BIOMARKER FOR THE SPECIFIC IMMUNE MICROENVIRONMENT OF GLIOMA

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INTRODUCTION: As recent advancement of multimodal treatments including immune-check point inhibitors have not led to massive outcome improvement of glioma. Targeting the peculiar immune microenvironment of glioma is a promising approach to innovate a breakthrough treatment, however, there remains to be technical and ethical burdens for monitoring the bioactivities of immune cells in neural tissues. Herein, we examined the feasibility of non-invasive monitoring of glioma-associated microglia/macrophages (GAM) properties through utilization of our originally developed induced-microglia-like (iMG) cells technique. METHODS: We isolated primary microglia (pMG) from surgically-obtained brain tissues of 15 patients with neurosurgical diseases. We induced iMG cells from monocyte extracted from their corresponding peripheral blood by MACS treatment. Expression profiles of representative markers for an M1 and M2 microglia phenotype were analyzed in both pMG and iMG cells by qPCR. RESULTS: q-PCR revealed that a significant correlation of expression level of microglial markers between pMG and the corresponding iMG in each patient. Synchronous upregulations of CD206 were exclusively detected in patients with glioma. CONCLUSION: The present study suggested that iMG cells can be a less-invasive monitor tool for disease-related bioactivity of microglia, thereby seem to be utilized as an intermedium for investigation of relationship between microglia and neuronal diseases including glioma. CD206 upregulation detected by iMG technique can surrogate the specific microenvironment of glioma surrounding tissues and might be utilized as a future biomarker of glioma

ADULT CLINICAL TRIALS/THERAPEUTIC STUDIES (ACT)

ACT-02

CHANGES IN RECURRENCE PATTERN AND PROGNOSIS OF GLIOBLASTOMA AFTER APPROVAL OF BEVACIZUMAB AS FIRST-LINE APPLICATION

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