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INTRODUCTION: Alkylating agents, including Temozolomide (TMZ) and CCNU (ACNU) have been widely accepted as a standard treatment in malignant gliomas. Several studies also demonstrated that BCNU wafer placement extended survival in glioblastoma patients. However, little study demonstrated gene-specific efficacy of BCNU local therapy in malignant gliomas. Herein, we investigated BCNU sensitivity for patient-derived primary cultured glioma cells. MATERIALS AND METHODS: From January 2017 to July 2019, 58 gliomas (grade III, IV) were tested genomic analysis and ATP-based cell viability after BCNU treatment. IDH1/2 mutation and TERT promoter mutation status was determined by Sanger sequencing. MGMT methylation status were evaluated by methylation specific PCR. RESULTS: Of 58 cases,10 cases (17.2%) and 32 (55.2%) cases harbored IDH1/2 mutation and TERT mutation (C228T, C250T), respectively. Among them, co-mutation was identified in 5/58 cases (8.6%). MGMT was methylated in 17/58 cases (29.3%). Interestingly, the presence of TERT promoter mutation was positively correlated with BCNU sensitivity, particularly in IDH1/2 wild-type tumors ($p<0.05$). In contrast, there was no significant relationship between TMZ sensitivity and IDH mutation/MGMT methylation status. CONCLUSION: Although sample size is small, our results imply TERT promoter mutations might be a predictive molecular marker for BCNU sensitivity in malignant gliomas. Since TERT mutations are located at two hot spot loci (C228T and C250T), vast majority of TERT promoter mutations can be evaluated during surgery, which may contribute tailored therapeutic strategy in malignant gliomas.

TB-06

MOLECULAR MECHANISM OF BRAIN TUMOUR FORMATION DRIVEN BY SUPRATENTORIAL EPENDYMOMA-SPECIFIC YAP1 FUSION GENES

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YAP1 fusion-positive supratentorial ependymomas predominantly occur in infants, but the molecular mechanisms of oncogenesis are unknown. Here we show YAP1-MAMLD1 fusions but not YAP1 wildtype are sufficient to drive malignant transformation of neural progenitors in the developing cerebral cortex in mice, and the resulting tumours share histo-molecular characteristics of human ependymomas. Nuclear localization of YAP1-MAMLD1 protein is associated with its oncogenicity and is mediated by the nuclear localization signal of MAMLD1 in a YAP1-Ser127 phosphorylation-independent manner. Chromatin immunoprecipitation-sequencing analyses of human YAP1-MAMLD1-positive ependymoma reveal enrichment of NFI and TEAD transcription factor binding site motifs in YAP1-bound regulatory elements, hypothesizing the important role of these transcription factors in YAP1-MAMLD1-driven tumourigenesis. Indeed, co-immunoprecipitation assays revealed physical interactions of TEADs and NFIA/B with the YAP1 and MAMLD1 domains of the fusion protein, respectively. Mutation of the TEAD binding site in the YAP1 fusion or repression of NFI targets prevents tumour induction in mice. Together, these results demonstrate that the YAP1-MAMLD1 fusion functions as an oncogenic driver of ependymoma through recruitment of TEADs and NFIs, indicating a rationale for preclinical studies to block the interaction between YAP1 fusions and NFI and TEAD transcription factors.

TB-08

PATIENT DERIVED XENOGRAFT'S BIOBANK FROM KANSAI MOLECULAR DIAGNOSIS NETWORK FOR CENTRAL NERVOUS SYSTEM TUMORS

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Patient-derived xenografts (PDXs) are essential tools for translational research for brain tumors. However, it is sometimes difficult for each institution to establish PDXs because it needs experiences and techniques and it also takes a lot of works to establish them. Thus we aim to establish patient derived xenograft's biobank among institutions of Kansai Molecular Diagnosis Network for Central Nervous System (CNS) Tumors, Osaka, Japan. We have already began sharing two anaplastic astrocytoma PDXs, twelve glioblastoma IDH wild type PDXs, two medulloblastoma Shh subgroup PDXs, one atypical teratoid/rhabdoid tumor (AT/RT) PDX, and three metastatic brain tumor PDXs. Furthermore these PDXs can also be cultured in vitro, except 2 medulloblastoma SHH subgroup PDXs, 1 AT/RT PDX. However, we have not yet established any PDXs from low grade glioma, ependymoma, primary central nervous system lymphoma (PCNSL), diffuse intrinsic pontine glioma (DIPG).

We began sharing these PDXs among the institutions of Kansai Molecular Diagnosis Network for CNS Tumors, Osaka, Japan. However, further improvement is necessary to succeed in establishing PDX from low grade glioma, PCSNL, DIPG, etc. and get enough number of PDXs so we can share PDXs from almost all of the brain tumors.

TB-09

MRNA-SEQ FOR PERICYTES FROM IN VITRO BRAIN METASTASIS AND BLOOD-BRAIN BARRIER MODEL.

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BACKGROUND: Metastatic brain tumors associated with poor prognosis and limited treatment options. The blood-brain barrier (BBB) is supposed to play a major role in brain metastasis. However, little is known about the role of pericytes in brain metastasis formation. This study aimed to reveal the expression profile of interaction between pericytes, endothelial cells, and cancer cells. METHODS: The Institutional review board approved this study. We established an in vitro BBB model with rat primary cultured BBB-related cells (endothelial cells and pericytes) and investigated the gene expression of pericytes under the lung cancer cell's coculture circumstances. Pericytes showed inhibition of the KNS-62 cell proliferation significantly ($p < 0.05$). RNA was extracted from the pericytes using miRNeasy mini kit. Complementary DNA library preparation was performed with QuantSeq 3 'mRNA-Seq Library Prep Kit. RNA-seq was performed with MiSeq using MiSeq Reagent Kit v3. Sequencing reads were analyzed on the Maser (TopHat2-CuffLinks2-CummeRbund, TopHat2-HTSeq) and TCC-GUI (EdgeR, DESeq, baySeq) platform. Enrichment analysis was performed at Metascape, and the results were analyzed concerning the OMIM and KEGG databases. RESULT: The RIN value of RNA < 8.0 was confirmed. Data quality was acceptable in Fast QC analysis. In TCC differential expressed gene (DEG) analysis, cluster analysis showed that the influence of pericyte lot difference was stronger than the change between cell lines and control. Therefore, lot-specific DEG analysis was performed; the data were pretreated and re-analyzed to try to identify genes involved in the suppression of cancer cell growth. DISCUSSION: This study revealed that some expression profiles of brain pericytes implemented in the prevention of metastatic lung cancer cell proliferation in the brain. Pericytes exert an anti-metastatic effect and thus have the potential for the preventive treatment of brain metastasis.

IMMUNOLOGY (IM)

IM-01

PI3K GAMMA INHIBITOR FOR OVERCOMING TREATMENT RESISTANCE IN COMBINATION THERAPY OF TEMOZOLOMIDE AND ANTI-PDL1 ANTIBODY FOR GLIOBLASTOMA PATIENTS

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PURPOSE: Multidisciplinary therapies including immunotherapy in glioblastoma (GBM) patients often cause long survivor, while early relapse of GBM still remains. We should find factors associated with the immunotherapy-resistance for overcoming it. We previously reported that the infiltration of PD-1 positive cells and M2 macrophages (M2M&phi) increased in recurrent specimens compared to the initial specimens of GBMs treated with chemo-radiotherapy and autologous formalin-fixed tumor vaccine. Here we evaluate whether combination of novel immunotherapies, anti-PD-L1 antibody and M2M&phi inhibitor (IPI-549) inhibits growth of temozolomide (TMZ)-treated glioma cells rather than monotherapy. METHODS: Using murine glioma initiating cells (TS) and TMZ-resistant TS (TMZRTS) cells, PD-L1 expression and cytokine production associated with M2M&phi were evaluated. TMZRTS cells were implanted in mice flank, followed by anti-PD-L1 antibody and / or IPI-549 administration. RESULTS: Relative cell proliferation rate of TMZRTS cells was lower than TS cells, while PD-L1 mRNA expression was higher. Treatment with PD-L1 antibody caused marked infiltration of M2M&phi in glioma tissue. The