ET-13

CONTROL OF ACTIVATED MICROGLIA THROUGH P2X4 RECEPTOR IN RADIATION BRAIN NECROSIS

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INTRODUCTION: Brain radiation necrosis (RN) is severe adverse event after radiation therapy for brain tumor patients, especially in case of re-irradiation. Although corticosteroids or vitamin E, etc. are clinically used for RN, the effect is limited and underlying mechanism is to be cleared. Therefore, we established RN mouse model with irradiating right hemisphere of mouse brain using proton beam at dose of 60 Gy [Kondo et al., 2015]. In this study, we investigated change of phospholipids and lipid mediators after irradiation using this RN model in correlation with microglia activation. METHODS: After irradiation, change of phospholipids and lipid mediators in mouse brain was investigated using imaging mass spectrometry and LC-MS. Immunohistochemistry on microglia and P2X4 receptor, a receptor for lysophosphatidylcholine (LPC) was performed. RESULTS: In imaging mass spectrometry, 1 and 4 months after irradiation, phosphatidylcholine (PC): (16:0/20:4), (18:0/20:4) decreased in irradiated area compared non-irradiated area. On the other hand, LPC: (16:0) increased in irradiated area compared to non-irradiated area after 1 month and 4 months irradiation. PC (16:0/20:4) is a precursor of LPC (16:0) and arachidonic acid (20:4). By LC-MS, LPC was twice higher in irradiated area compared to non-irradiated, 6 months after irradiation. Microglia was highly activated in irradiated area compared to non-irradiated from 3 months after irradiation to 8 months and strongly co-expressed P2X4 receptor was confirmed in irradiated area after 6 months. Preliminary P2X4 receptor agonist administration test prolonged the RN to 12 months after irradiation. CONCLUSION: In RN, LPC may continuously activated microglia through P2X4 receptor and cause chronic inflammation after irradiation. P2X4 agonist administration test including action resolution and immunohistochemistry is ongoing.

TUMOR BIOLOGY/MODELS (TB)

TB-01

HUMAN IPS CELL-DERIVED BRAIN TUMOR MODEL UNCOVERS THE EMBRYONIC STEM CELL SIGNATURE AS A KEY DRIVER IN ATYPICAL TERATOID/RHABDOID TUMOR

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Atypical teratoid/rhabdoid tumor (AT/RT), which harbors SMARCB1 mutation and exhibits a characteristic histology of rhabdoid cells, has a poor prognosis because of the lack of effective treatments. We established human SMARCB1-deficient pluripotent stem cells (hPSCs), which enabled investigation of the pathogenesis of AT/RT. SMARCB1-deficient hPSCs and neural progenitor-like cells (NPLCs) efficiently gave rise to brain tumors when transplanted into mouse brain. Notably, the emergence of typical rhabdoid cells was significantly enhanced in tumors from SMARCB1-deficient hPSCs. An embryonic stem cell (ESC)-like gene expression signature was more prominent in hPSC-derived tumors when compared with NPLCs-derived tumors. Moreover, mice transplanted with SMARCB1-deficient hPSCs showed poor survival than NPLC-transplanted mice. Activation of the ESC-like signature by the forced expression of reprogramming factors conferred a rhabdoid histology in SMARCB1-deficient NPLC-derived tumors, suggesting that acquisition of the ESC-like signature is responsible for the rhabdoid histology. Consistently, we found activation of the ESC-like gene expression signature and an ESC-like DNA methylation landscape in clinical specimens of AT/RT. Mechanistically, c-MYC expression was sufficient to acquire the ESC-like signature and the rhabdoid histology in SMARCB1-deficient NPLC-derived tumors, which resulted in poor survival. Together, SMARCB1-deficient hPSCs offer the first human model for AT/RT, which uncovered the unappreciated role of the activated ESC-like signature in the poor prognosis and unique histology. Finally, we performed a CRISPR/Cas9 knockout screening to inhibit activation of the ESC-like signature in AT/RT. Our effort identified candidate genes as therapeutic targets, including RAD21, which encodes a key component within the cohesin complex. Notably, chemical inhibition of HDAC8, which indirectly targets the function of cohesin, with simultaneous inhibition of EZH2 efficiently suppressed activation of the ESC-like signature and inhibited the growth of AT/RT cells. Collectively, we propose that the ESC-like signature could be a crucial therapeutic target for AT/RTs with rhabdoid histology.

TB-02

NF-KB CANONICAL PATHWAY ACTIVATION DRIVES GLYCOLYSIS AND TUMOR PROGRESSION IN PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA

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Recent genomic analyses have identified highly recurrent genetic alterations in PCNSL. However, due to the lack of clinically representative PCNSL preclinical models, the pathogenic mechanisms of these alterations remains largely unknown. Here, we established the largest panel of 12 clinically relevant PCNSL patient-derived orthotopic xenografts retained the histopathologic phenotype, lymphoma expression subtype, copy number alterations and 90% of the non-synonymous mutations of primary tumors, with 100% concordance of MYD88 and CD79B mutations, which are highly recurrent in PCNSL. Patient tumor regression with high-dose methotrexate correlated with in vitro sensitivity to methotrexate in corresponding PCNSL models. By knocking down canonical NF-kB pathway genes, we found that successful orthotopic xenograft formation was dependent on NF-kB canonical pathway activation induced by MYD88 mutation or overexpression of EBV-related LMP1. Metabolically, PCNSL xenografts phenocopied the high 18F-fluorodeoxyglucose uptake observed in patients and demonstrated glycolytic dependence, revealing new potential therapeutic strategies in PCNSL. Collectively, we found NF-kB canonical pathway activation as a crucial driver of PCNSL xenograft progression and found that NF-kB canonical pathway induced an addiction to glycolysis, revealing a novel potential therapeutic strategy. Our PCNSL xenograft panel represents a valuable and reproducible preclinical tool that has the potential to help decipher how genetic and/or epigenetic alterations contributes to lymphomagenesis and tumor maintenance and enhance the development of novel therapeutic strategies in PCNSL.

TB-03

THE SURVIVAL PROLONGATION EFFECT OF NOVEL BORON COMPOUND FOR BNCT USING RAT BRAIN TUMOR MODEL

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INTRODUCTION: Boron neutron capture therapy (BNCT) is form of tumor-cell selective particle irradiation. Although novel boron compounds have been developed, BPA (boronophenylalanine) and BSH (borocaptate sodium) are used in the clinical practice. The development of effective boron compounds is a major theme. We used Dodecaborate-containing BPA (AAL) which is combined the characteristics of both BPA and BSH. We have been conducting research on how the new compound for BNCT will affect rat brain tumor model. MATERIALS AND METHODS: We evaluated the boron concentration of F98 glioma cells for BPA and AAL, and the biodistribution of these following BPA administrated intravenously (i.v.) or AAL administrated by convection-enhanced delivery (CED) in F98 glioma bearing rats. In BNCT study, the therapeutic effect was evaluated in terms of the survival time for all rats divided into six groups. RESULTS: The uptake of boron showed almost the same value at all exposure times in high concentration. In biodistribution study, the AAL(CED) 6h after the termination group attained the highest boron concentrations of the tumor (59.9 ± 18.2 μg/g). In the BNCT study, the median survival time in the AAL(CED) group (31(29–35) days) was shorter than that in the BPA(i.v.) group(34(33–36) days). And the combination group of AAL(CED) and BPA(i.v.) gave the most significant prolongation of survival(38(36–40) days). DISCUSSION: AAL(CED) and BPA(i.v.) combined group had a significant survival prolongation compared with the single-agent group. It is thought that AAL irradiated by thermal neutron had a cell-killing effect on cells in which BPA was not taken up. The combination uses of AAL (CED) provides additional BNCT effects. The mechanism by which AAL is incorporated has not been clarified, and further experiments including the influence on normal cells are in progress. CONCLUSION: Dodecaborate-containing BPA (AAL) is a novel boron compound for BNCT that can be expected to prolong the survival time in combination with BPA.

TB-04

TERT PROMOTER MUTATION AS A SUSCEPTIBLE MOLECULAR MARKER OF BCNU LOCAL THERAPY

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