with reduced expression of this molecule by MEK inhibitor trametinib suppressed augmented proliferation of these cells. Taken together, these results suggest that protein ubiquitination-related pathways as well as MEK-ERK cascade may serve as a novel therapeutic target against NGGCTs.

CBMS-12

PRO RENIN RECEPTOR ANTIBODY REGULATES GLIOBLASTOMA STEMNESS

Takeshi Fujimori[1], Daisuke Oagawa[1], Takahiro Kanda[1], Kenta Suzuki[1], Saki Shibayama[2], Keisuke Miyake[1], Akira Nishiyama[2], Takashi Tamiya[1]; [1]Department of Neurological Surgery, Kagawa University Faculty of Medicine

OBJECTIVE: Glioblastoma multiforme (GBM) is characterized by a strong self-renewal potential and poor differentiated state. We previously reported that (pro)renin receptor (PRR) was a potential target for glioma therapy by silencing the gene of PRR. Here, we have developed the monoclonal antibody of PRR and examined their effects on GBM. Materials and METHODS: We performed immunohistochemical analysis to detect the protein expression of PRR and SOX-2 in human sample of 56 gliomas. We used human glioma cell lines (U251MG and U87MG) and glioma stem cell line (MGG23) in vitro study. PRR antibody was designed to target the extracellular domain of the PRR with the rat lymph node method. Expression of the Wnt signaling components and stem marker (SOX-2, Oct3/4) in human glioma cell lines and glioma stem cell line treated with PRR antibody were measured using Western blotting. The effects of PRR antibody on cell proliferation, sphere formation, apoptosis, invasion were also examined. Subcutaneous xenografts with U87MG were induced in nude mice. RESULTS: PRR expression showed a positive correlation with SOX-2 expression in glioma samples. Treatment with PRR antibody significantly reduced expression of Wnt signaling components and stem marker. We observed that PRR antibody significantly reduced cell proliferation and decreased sphere formation. Furthermore, PRR antibody suppressed invasion and induced apoptosis. In a subcutaneous U87MG xenograft model, systemic administration of the PRR antibody significantly reduced the size of the tumor volume. CONCLUSION: PRR has important role for the maintenance of stem cells and contribute to stem cell proliferation. PRR antibody inhibits cell proliferation and cell invasion and induces apoptosis. Treatment with PRR antibody could be an attractive therapeutic strategy for GBM.

SIGNALING PATHWAYS/DRUG RESISTANCE (SPDR)

SPDR-01

PAIRED EPITHELIOID GLIOBLASTOMA PATIENT-DERIVED XENOGRAFT MODELS TO EVALUATE RESISTANT MECHANISM FOR MOLECULAR TARGET THERAPY

Jo Sasame[1], Kensuke Tateishi[1], Naoki Ikegaya[1], Yohei Miyake[1], Taishi Nakamura[1,3], Naoko Udaka[2], Shoji Yamanaka[2], Tetsuya Yamamoto[1]; [1]Department of Neurosurgery, Yokohama City University, Graduate School of Medicine, Yokohama, Japan

Epithelioid glioblastoma (E-GBM) arises at younger age, commonly disseminates to cerebrospinal fluid, and results in dismal prognosis. About half of E-GBM harbors *BRAF* V600E mutation, thus BRAF/MEK inhibitors are expected to be specifically sensitive to E-GBM like other *BRAF* V600E mutant carcinomas. However, therapeutic effect is limited by the emergence of drug resistance. To overcome this issue, it is crucial to elucidate the treatment resistance mechanisms by clinically representative models. Herein, we establish 2 paired E-GBM patient-derived xenograft (PDX) models from young adult patients (YMG62 and YMG89) with *BRAF* V600E, *TERT* promoter mutations and *CDKN2A* homozygous deletions. The YMG62 patient received dabrafenib with trametinib, while YMG89 patient received dabrafenib monotherapy after recurrence with standard treatment. The YMG62 patient was refractory to combination therapy. The YMG89 patient was initially responded to dabrafenib, but gradually became resistant and the 2 patients died due to CNS dissemination. Paired PDX models were established from tumors prior and after molecular target therapy. All PDXs were formed as CNS dissemination model, which were recapitulated to the patient characteristics. BRAF/MEK inhibitors strongly suppressed cell viability in primary tumor (YMG89P). However, BRAF/MEK inhibitors became resistant in recurrent tumor (YMG89R). YMG62 paired PDXs were resistant to molecular target therapy. Western blotting indicated retained MAPK signaling pathway and/or increased AKT phosphorylation after BRAF/MEK inhibitors treatment in refractory and recurrent cells, which indicates crucial role of re-activation in the MAPK signaling pathway and/or PI3 kinase pathway for tumor maintenance in *BRAF* V600E mutant E-GBM. We have done high throughput drug screening to identify compounds to overcome resistant to molecular target therapy. Our established E-GBM paired PDX models recapitulate patient characteristics, which may uncover treatment resistant mechanism and novel therapeutic target in E-GBM.

GENETICS/EPIGENETICS (GEN)

GEN-09

PURSUING THE FUNCTION OF MICRORNA TARGETING (PRO) RENIN RECEPTOR AGAINST GLIOMA

Daisuke Ogawa[1], Takeshi Fujimori[1], Yasunori Toyota[1], Tetsuhiro Hatakeyama[1], Masanobu Okauchi[1], Masahiko Kawanishi[1], Keisuke Miyake[1], Tsutomu Masaki[2], Akira Nishiyama[3], Takashi Tamiya[1]; [1]Department of Neurosurgery, Kagawa University, Japan

(Pro)renin receptor((P)RR) is a part of the Wnt receptor complex. Wnt/β-catenin signaling pathway (Wnt signaling) plays important role in pathogenesis and self-renewal of glioblastoma (GBM), or differentiation of glioma stem cell. We previously reported that (P)RR activated Wnt signaling, (P)RR expression correlated with malignancy of glioma, and treatment with (P)RR siRNA reduced the proliferative capacity. This time, we have searched for over 2632 microRNAs by microRNA microarray that its expression is affected by (P)RR whether overexpressed or suppressed and examined their effects in GBM cell lines or its glioma stem cells.

GEN-14

DUAL REGULATION OF HISTONE METHYLATION BY MTOR COMPLEXES DRIVES THE PROGRESSION OF EGFR-MUTANT GLIOBLASTOMA

Kenta Masui[1], Mio Harachi[1], Yoshihiro Muragaki[2], Paul Mischel[3], Noriyuki Shibata[1]; [1]Department of Pathology, Division of Pathological Neuroscience, Tokyo Women's Medical University, Tokyo, Japan

Trimethylation of histone H3 on lysine 27 (H3K27me3) is essential for ensuring proper gene expression and chromosomal function, and its aberration is associated with the pathogenesis of various brain tumors. However, it remains unclear how histone methylation is regulated in response to genetic mutation and intracellular metabolic status to facilitate the cancer cell survival in the most malignant IDH-wildtype glioblastoma (GBM). We herein report a novel mechanism of the specific regulation of H3K27me3 by cooperative action of two mechanistic target of rapamycin (mTOR) complexes in EGFR-mutant GBM. The level of H3K27me3 is significantly associated with the mutant EGFR signaling (EGFRvIII and EGFR amplification), and integrated analyses with histopathological, NGS and metabolome examinations revealed that both mTOR complexes (mTORC1 and mTORC2) upregulate H3K27me3 downstream of aberrant EGFR signaling. mTORC1 facilitates the protein translation of enhancer of zeste homolog 2 (EZH2), which is known as H3K27-specific methyltransferase. The other mTOR complex, mTORC2, remodels the metabolism of S-adenosylmethionine (SAM), an essential substrate for histone methylation. This synergistic mechanism causes H3K27 hypermethylation which subsequently promotes tumor cell survival both in vitro and in vivo mouse tumor model via regulation of the cell cycle-related tumor suppressor genes. The findings indicate that activated mTORC1 and mTORC2 complexes under aberrant EGFR signaling cooperatively contribute to the progression of IDH-wildtype GBM through specific epigenetic regulation, nominating them as an exploitable therapeutic target against cancer-specific epigenetics.

EXPERIMENTAL THERAPEUTICS (ET)

ET-03

CONVECTION-ENHANCED DELIVERY OF EZH2 INHIBITOR FOR THE TREATMENT OF DIFFUSE MIDLINE GLIOMA

Takahiro Sasaki[1,2], Hiroaki Katagi[2], Becker Oren[3], Goldman Stewart[3], Naoyuki Nakao[1], Rintaro Hashizume[2]; [1]Department of Neurological Surgery, Wakayama Medical University

BACKGROUND: Diffuse midline glioma (DMG) is a fatal childhood brain tumor and the majority of patients die within 2 years after initial diagnosis. Factors that contribute to the dismal prognosis of these patients include the infiltrative nature and anatomic location in an eloquent area of the brain, which precludes total surgical resection, and the presence of the blood-brain barrier (BBB), which reduces the distribution of systemically administered agents. Convection-enhanced delivery (CED) is a direct infusion technique to deliver therapeutic agents into a target site in the brain and able to deliver a high concentration drug to the infusion site without systemic toxicities. OBJECTIVE: This study aims to assess the efficacy of enhancer of